CONGENITAL CARDIOLOGY TODAY

Timely News and Information for BC/BE Congenital/Structural Cardiologists and Surgeons

Volume 10 / Issue 7
July 2012
International Edition

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CONGENITAL CARDIOLOGY TODAY
Editorial and Subscription Offices
16 Cove Rd, Ste. 200
Westerly, RI 02891 USA
www.CongenitalCardiologyToday.com

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Biodegradable Devices for the Treatment of Congenital Cardiovascular Disease

By Daniel S. Levi, MD and Andrew L. Cheng, MD

Although biodegradable materials have been used in medicine for several decades, these materials only recently have been utilized for pediatric transcatheter and surgical vascular and cardiac devices. Most devices used to repair congenital heart lesions only need to serve as temporary scaffoldings; ideally, they would ultimately disappear.

Biodegradable implants have many potential advantages over conventional devices. The interest in these materials for pediatric applications is primarily to accommodate growth. Lesions such as coarctation of the aorta and pulmonary artery stenosis could be temporarily augmented with a bioresorbable stent, allowing time for remodeling. As the patient grows and the vessel regains adequate functionality, the stent is slowly resorbed. Eventual complete resorption of the stent avoids the complications associated with traditional stents and eliminates the possible need to remove the device in the future.

Biodegradable devices for congenital heart patients can also facilitate other interventions at the same site. Biodegradable stents and devices will completely avoid these "full metal jacket" situations and may even preserve side branches near the site of intervention. These devices also will allow for improved radiographic imaging of lesions with MRI or CT.

> ***"Biodegradable implants have many potential advantages over conventional devices. The interest in these materials for pediatric applications is primarily to accommodate growth."***

Reduction or avoidance of late stent restenosis has been ascribed, at least to some degree, to inflammation around metallic struts after coronary stenting. Replacement of the conventional metallic scaffold with an absorbable biopolymer, therefore, theoretically should decrease the rate of restenosis. This has been the impetus for the maturation of biodegradable stent technology and currently a variety of biodegradable coronary stents are now being tested in the adult population. As many bioresorbable stents are embedded with drug-eluting agents, they may even provide an opportunity to improve results in stenting difficult lesions such as pulmonary vein stenoses.

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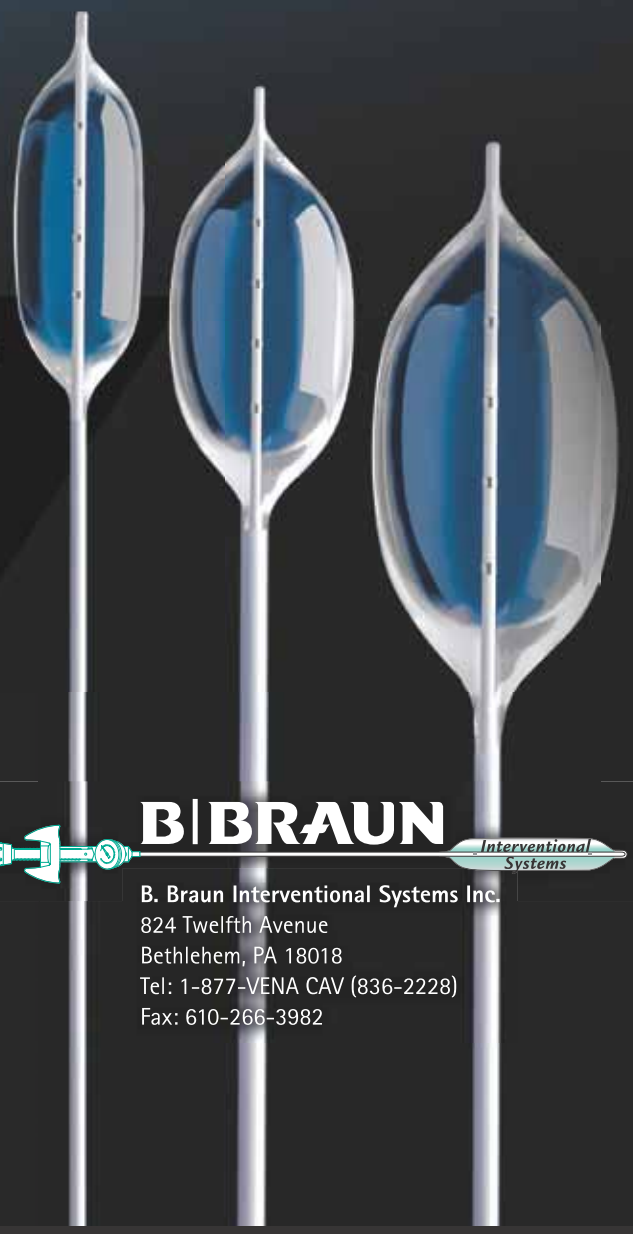

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Table 1
Comparison of Biodegradable Stents That Have Undergone Clinical Trials in Humans: BTI Bioabsorbable Therapeutics Inc., BVS Bioresorbable Vascular Scaffold, AMS Biotronik Absorbable Bagnesium Stent, PLLA Poly (L-lactic acid), PDLLA Poly (D,L-lactic acid)

Stent	Material	Coating	Design	Byproducts	Drug elution	Radio-opacity	Strut thickness, µm	Crossing profile, mm	Stent-to-artery coverage, %	Radial support duration	Absorption time
Igaki-Tamai	PLLA	None	Zig-zag helical coils with straight bridges	Lactic acid, CO_2, H_2O	None	Gold markers	170	?	24	6 months	2 years
REVA	Poly(12DT E-12DT carbonate)	None	Slide and lock	L-tyrosine, ethanol, CO_2	None	Iodine impregnated	200	1.7	55	3-6 months	2 years
BTI	Salicylate + linker polymer	Salicylate + adipic acid	Tube with laser-cut voids	Salicylate, CO_2, H_2O	Sirolimus, salicylate	None	200	2.0	65	3 months	6 months
BVS	PLLA	PDLLA	1.0: out-of-phase sinusoidal hoops with straight and direct links. 1.1: in-phase hoops with straight links	Lactic acid, CO_2, H_2O	Everolimus	Platinum markers	156	1.4	25	1.0: weeks. 1.1: 3 months	2 years
AMS	Magnesium alloy	None	Sinusoidal in-phase hoops linked by straight bridges	N/A	None	None	165	1.2	10	Days-weeks	<4 months

Biodegradable Stents

Biodegradable stents have been the most heavily investigated biodegradable cardiovascular devices to date. These devices have been hypothesized to cause a decreased incidence of late thrombosis, since they are eventually completely resorbed. The new generation of fully absorbable stents will, hopefully, minimize or completely eliminate late restenosis.

Like other drug-eluting stents (DES), biodegradable stents have the ability to deliver antiproliferative medications, such as sirolimus, directly to the site of disease. In the pediatric population, such devices may be particularly valuable for systemic or pulmonary vein stenting, as restenosis in this setting is extremely common.

Several biodegradable stents that have undergone clinical trials are discussed below (Table 1).

Igaki-Tamai Stent

The Igaki-Tamai stent was the first absorbable stent to be implanted in a human. It is made from poly(L-lactic acid) (PLLA). Strut thickness and vessel coverage by the struts both are larger than conventional metal stents (Figure 1a). Absorption is by bulk erosion and results in release of lactic acid, which is metabolized through the Krebs cycle.

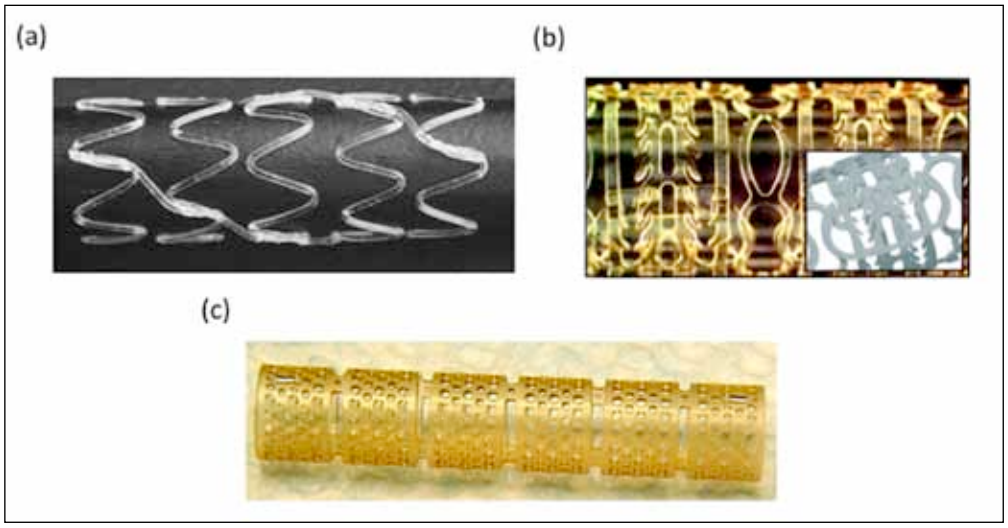

Figure 1: Biodegradable Stents. (a) The Igaki-Tamai stent, (b) the REVA stent, (c) the BTI Stent.

A first-in-man prospective nonrandomized clinical trial of the stent was performed in 50 patients with a low complication rate. Although no further human coronary implants have been performed with this stent, it is being explored for peripheral applications and is clearly the predecessor to the current generation of coronary and peripheral biodegradable stents.

REVA Stent

The REVA stent is made from an absorbable tyrosine-derived polycarbonate polymer, configured in a slide and lock (ratchet) structure that allows for expansion without deformation (Figure 1b). This design may allow for increased radial force in stents designed for pulmonary artery and coarctation stenting. The RESORB first-in-man trial was a prospective nonrandomized safety study with a non-drug-eluting version of the REVA stent. Poor outcomes were noted with higher-than-anticipated target lesion revascularization due mainly to reduced stent diameter. A susbsequent iteration of this stent, the ReZolve stent, includes an antiproliferative agent and soon will be undergoing clinical testing in the RESTORE trial.

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BTI Stent

The BTI stent is a bioabsorbable sirolimus-eluting stent. This device incorporates a polymer backbone made from repeating salicylate molecules (Figure 1c). Resorption of the device releases salicylic acid, which is anticipated to decrease the inflammation associated with PCI. The Whisper first-in-man trial of patients implanted with the BTI stent showed higher-than-expected neointimal hyperplasia. Thus, the design is currently being revised to include thinner struts, decreased wall coverage, and a higher dose of sirolimus.

BVS Everolimus-Eluting Stent

The Bioresorbable Vascular Scaffold (BVS) everolimus-eluting stent is the first biodegradable stent to have comparable clinical and imaging outcomes to metallic DES 2 years after implantation (Figure 2a). The BVS stent is composed of a PLLA backbone with a coating of poly(D,L-lactic acid) (PDLLA) and the antiproliferative drug everolimus. A larger version of this stent – possibly one designed for peripheral interventions – could be the first stent widely used for palliation of congenital heart disease.

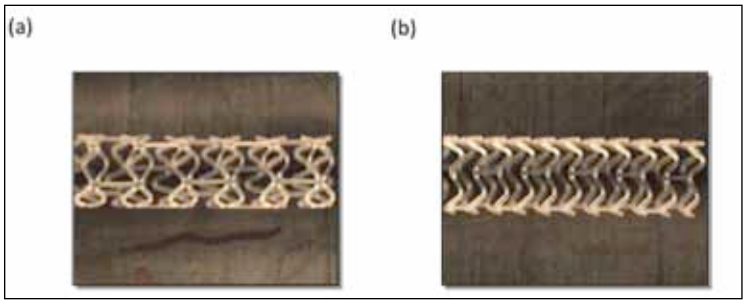

Figure 2: The BVS everolimus-eluting stent. (a) BVS 1.0, (b) BVS 1.1.

The ABSORB trials studied two different revisions of the stent. The ABSORB cohort, a first-in-man trial, was a prospective nonrandomized study of BVS stent revision 1.0. At 3 years post-implantation the ischemia-driven major adverse cardiac event rate was very favorable and there were no stent thromboses. No vessel shrinkage was seen at 6 months; however, angiographic late loss was similar to some metallic DES (Figure 3). Despite this shrinkage, the stent resisted negative remodeling well. In fact, between 6 months and 2 years lumen enlargement was detected. Vasoactivity in the stented segment was also noted in the small number of patients who were tested. These vessels showed vasoconstriction induced by methylergonovine maleate and vasodilatation induced by nitroglycerin. This observation suggests that the return of a physiologic response to vasoactive stimuli and the potential for arterial dilation in response to local ischemia is possible with bioresorbable stents.

The ABSORB cohort B trial is a prospective nonrandomized study of BVS stent revision 1.1. Based on results seen with BVS 1.0, modifications were made to maintain the mechanical integrity of the stent up to 6 months with the goal of reducing scaffold shrinkage and eventual late luminal loss, and to reduce acute and late recoil. The overall performance of BVS 1.1 at 6 months was significantly improved over BVS 1.0.

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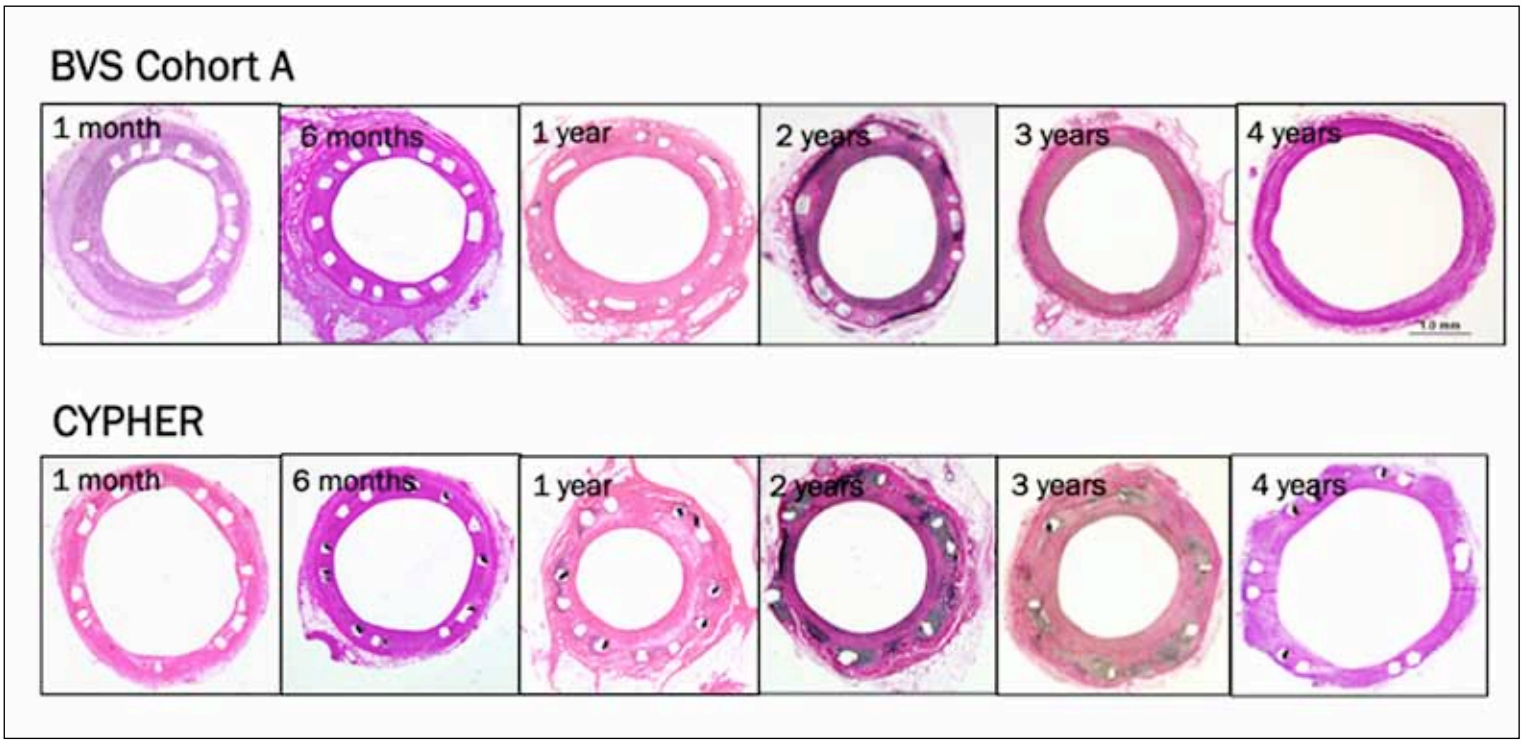

Figure 3: Histologic comparison of BVS 1.0 and Cypher stents in porcine model. The neointimal response was comparable between the two implants at 28 and 90 days in terms of neointimal composition and coverage. At later time points, however, the neointimal response to BVS stents was milder.

The ABSORB EXTEND trial is a single-arm study currently enrolling patients throughout Europe, Asia, Canada, and Latin America. The trial will include patients with more complex coronary artery disease than those in the previous ABSORB cohorts.

Biocorrodible Materials

Corrosion is a design consideration that must be taken into account for any metallic implant. It can lead to premature device failure and can affect biocompatibility by releasing metal ions/particles. While typically a hindrance that must be carefully combated, this property is now being investigated for positive uses. Biocorrodible metallic implants have the mechanical advantages of stainless steel, while also incorporating the benefits of a temporary scaffold like the previously described biodegradable devices.

Absorbable Magnesium Stent

The absorbable magnesium stent (AMS) was the first metallic bioabsorbable stent to be implanted in a human. The device is laser cut from tubular magnesium WE-43 (Figure 4). Arterial wall coverage is comparable to that of conventional BMS. Initial radial strength is similar to stainless steel stents. It is radiolucent and lacks radio-opaque markers. Absorption is by surface erosion, so strut thickness decreases as the stent is absorbed.

The PROGRESS-AMS trial was a prospective nonrandomized study of 63 patients with simple de novo native coronary artery lesions in whom magnesium stents were implanted. Angiographic results immediately after implantation were similar to those seen with conventional BMS. Radial support, however, was lost very early, and accordingly there was a high restenosis rate of almost 50% at 4 months.

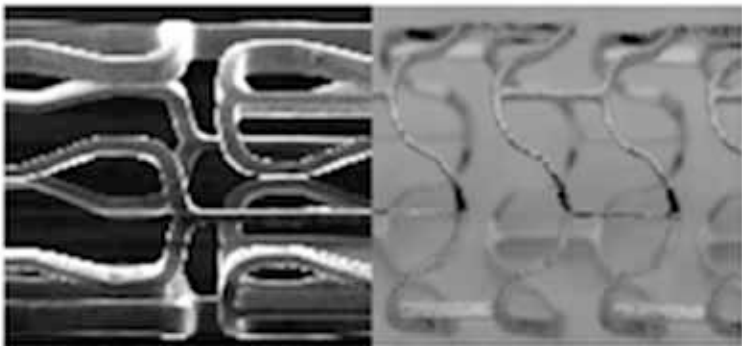

Figure 4: The Biotronik absorbable magnesium stent.

While the AMS stent is clearly not ideal for use in coronary applications, it may be well suited for pediatric applications. The AMS was successfully implanted in two newborns for emergency off-label uses. Its first use was in a 6 week-old female baby who had been born prematurely at 26 weeks gestation. In this case, the AMS was used to correct an accidental ligation of the left pulmonary artery. At 5 months, after the stent had been completely degraded, left lung perfusion remained adequate. The second pediatric application of the AMS was in a 3 week-old male baby with a postsurgical long-segment recoarctation. This patient also did well with the stent and did not require further intervention until 3 months later.

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Summary

Because of their use in coronary stents, biodegradable polymers have been developed for use in medical devices. Biodegradable stents and closure devices are in clinical trials. The chemistry and mechanical properties of these materials are well known. It is possible to engineer devices with very predictable degradation times, biology and radial force. Biodegradable materials are likely to replace many of the conventional metals in the current surgical and transcatheter pediatric devices. In general, the ideal material will always need to be non-toxic, non-thrombogenic, and will need to have appropriate strength, elasticity and degradation rate. Because the ideal biodegradable material will need to be tailored from device to device, there is unlikely to ever be one "ideal" biodegradable material. Nonetheless, many challenges remain for the development of devices in the pediatric community. A wide range of potential biodegradable devices can be realized in the pediatric community if the significant biological, regulatory and financial issues in bringing new pediatric biodegradable devices to market can be overcome.

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Biographical Sketch of Principal Author

Daniel S. Levi, MD is an Interventional Pediatric Cardiologist who has served on the UCLA School of Medicine faculty since 2003. His primary clinical role involves the use of catheters and devices to help children with congenital heart disease. He is internationally known for his laboratory and clinical research. He is also the director of the adult congenital interventional catheterization program and director of the fellowship program in pediatric cardiology, and is a member of the pediatric heart transplantation team.

Dr. Levi earned his B.S. in Biology from Stanford (1992) and his M.D. from UCSF (1997). He was in the Medical Scientist Training Program at UCSF from 1992-1995. After Pediatrics internship and residency were completed at UCSF, Dr Levi completed his pediatric cardiology fellowship and pediatric interventional cardiology sub-specialization at UCLA. He is board certified in Pediatric Cardiology by the American Academy of Pediatrics, he is the recipient of the Gerd Hausdorf Pediatric Research Award and is director of the Congenital Program of the Society for Cardiac Angiography and Interventions (SCAI) annual program. His laboratory research centers on the development of novel pediatric stents and other devices made from nano-synthesized "smart" materials such as thin film nitinol. Dr. Levi is been the recipient of grants from the National Institue of Health (NIH), National Science Foundation (NSF), the American Heart Association (AHA), the Paige Foundation and multiple other foundations and agencies.

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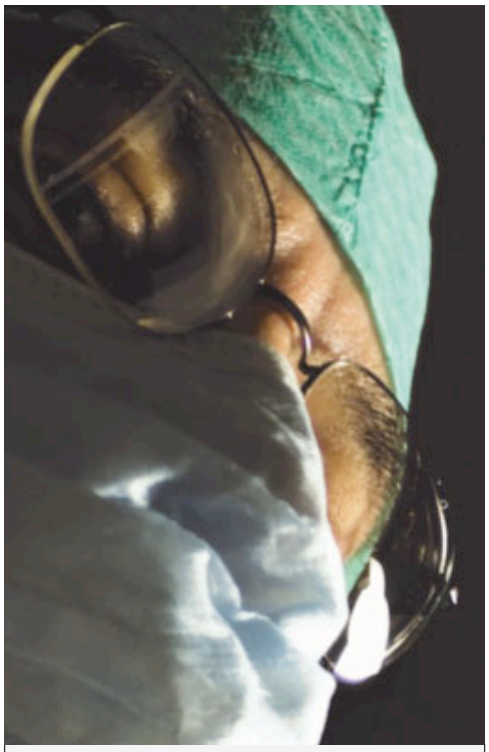

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Highlights of Inaugural Breakout Session of PICES (Pediatric/Congenital Interventional Cardiology Early-Career Society) at SCAI's Annual Meeting

By Brent M. Gordon, MD

The Pediatric/Congenital Interventional Cardiology Early-Career Society (*PICES*) held its inaugural breakout sessions at both the *PICS/AICS* and *SCAI* conferences in 2012. *PICES* was established in July of 2011, and is currently a task force under the umbrella of the Congenital Heart Disease council of *SCAI*. The group was established to support and advance the careers of young interventionalists in structural heart disease. The *PICES* group has several goals including: clinical education, multi-center research collaboration, improving transcatheter treatment of congenital heart disease in developing countries, and creation of a social network. The *PICES* executive board is composed of president Daniel H. Gruenstein, MD, from University of Minnesota, Amplatz Children's Hospital; clinical chair Brent M. Gordon, MD, from Loma Linda University Children's Hospital; research chair Michael A. Bingler, MD, from Children's Mercy Hospital, Kansas City; and secretary John S. Lozier, MD, from Pediatric Cardiology PC, Mercy Medical Center, Des Moines, Iowa.

The breakout session at PICS began with a welcome from Dan Gruenstein, followed by a guest lecture from Henri Justino, MD, from Texas Children's Hospital entitled, "Creating a Career Niche-Revascularization of Thrombosed Vasculature in Pediatric Patients." Dr. Justino profiled several truly remarkable outcomes in neonates and children with life-threatening vascular thromboses and discussed several modalities available to treat this difficult subset of patients. The talk concluded with suggestions and philosophies that young interventionalists may utilize to help establish a career niche for themselves. This was followed by case presentations from Bryan Goldstein, MD, and Nathaniel Taggart, MD. Dr. Goldstein discussed a case of severe aortic coarctation with associated aneurysmal involvement of the left subclavian artery that was treated with a covered CP stent, while Dr. Taggart presented an example of transcatheter Fontan completion. The cases generated healthy discussion from the audience and lent themselves to numerous teaching points.

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The *PICS* meeting also featured the inaugural selection of the Young Leadership Program for early career interventionalists. Christopher Petit, MD, from Texas Children's Hospital and a PICES member, was selected as the initial recipient. Dr. Petit was designated a faculty member for the meeting and had the opportunity to chair several sessions throughout the meeting while participating with the other faculty. *PICES* was very involved in creating the Young Leader Program and congratulates Dr. Petit on all of his accomplishments.

The *PICES* group also had a significant presence at SCAI that culminated in a breakout session on Friday afternoon. The session began with a talk by Lynn Peng, MD, from Lucille Packard Children's Hospital at Stanford University on the Emerging Leadership Mentoring (ELM) Program. The ELM program, of which Dr. Peng is currently the only pediatric interventional representative, was created by SCAI to pair young interventionalists with senior mentors, with the ultimate goal of training younger faculty to become the leaders of tomorrow in the treatment of structural heart disease. The next series of ELM applications will be due in the fall of 2012. Please see the SCAI website for further information.

The breakout session continued with several interesting case presentations. Jeffery Zampi, MD from University of Michigan discussed transcatheter Fontan fenestration creation, Luke Lamers, MD from Phoenix Children's Hospital showed a coronary artery fistula case with some bonus operator chest pain, and Michael Bingler, MD discussed the utility of balloon angioplasty in the treatment of discrete subaortic membrane. After a close vote, Dr. Lamer's case was deemed the best presentation and he received the inaugural PICES case presentation award, which he will watch over until the next meeting. Congratulations Dr. Lamers for a job well done.

The *PICES* membership is now approaching 80 people with representatives from the United States and several other countries around the world. We plan to have a link to our website operational within the next few months and are excited to initiate some multi-center studies before the end of summer. The next formal meeting will be in January 2013 at *PICS* in Miami. Nominations for future board members will be accepted at that time with elections to follow at *SCAI* in Orlando. For further information or to be added to the *PICES* list-serve please contact John Lozier at: john.lozier@gmail.com.

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China California Heart Watch

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The China California Heart Watch Looking for Participants for Several Internships

The China California Heart Watch is a not-for-profit public charity whose missions include medical research, teaching and clinical care in rural Yunnan Province, China. They invite students, particularly those interested in future careers in medicine, public health or related fields to participate in one of several internships this year. These internships involve first-hand exposure to medical problems – particularly cardiovascular problems – and care in impoverished communities, where access to high-quality medical services is very limited.

Objective: The objective of the internship program is to create awareness of the problems of healthcare in rural China, and encourage students to pursue a career in public health and/or medicine focused on the underserved in developing countries.

Students: China Cal will have three internship programs for the remainder of 2012. Each is open to 5-15 students. Candidates will be interviewed to determine suitability. To intern at China Cal, you must have an interest in pursuing a career involving public health or health-related care in underserved populations. Some knowledge of Mandarin is desirable, although this is not a strict requirement.

August-December 2012 upcoming Internship dates: August 4th – 26th; September 1st – 23rd; and December 14th – 30th.

Programs: Upon arrival in Yunnan (Kunming or Dali), students will undergo three days of training and certification. Students will learn about how to assist in a program focuses on screening and treatment of adults and school children living in rural towns, who have hight blood pressure and heart disease. We then travel to surrounding areas to begin clinics among rural populations. Interns will travel and work alongside with faculty members from Kunming and Dali Universities, as well as receiving training from Dr. Robert C. Detrano, MD, PhD, Professor of Radiological Sciences at the University of California at Irvine and a board-certified cardiologist. Interns will also have the opportunity to help conduct a clinical research program while staying in villages in Yunnan. To read experiences of recent interns, please visit: www.chinacal.org.

Logistics: Students will travel to Yunnan Province, where several China Cal staff will meet the students at the airport. China Cal will arrange all accommodations, as well as any local travel (by bus, train or air as needed). Students will be living in hotels, community centers and, occasionally while in remote areas, the homes of farmers.
Students are required to cover the cost of all travel expenses to, from and within China, as well as room and board. China Cal also requests a tax-free donation of US$2000 for all summer programs or US$1500 for the December program. This donation helps fund China Cal's charitable activities, including training village doctors, acquiring medical equipment, and conducting hypertension research. Foreigners require a valid visa to enter China. This must be organized though agencies or the Chinese consulate/embassy in the student's home country.
Health and Safety: Yunnan Province is a relatively safe place for foreign visitors. Students will be advised regarding caution and care for their belongings and documents. Health risks are relatively few. However, as visitors sometimes suffer from gastroenteritis, China Cal doctors will provide prophylactic education, and medications will be on-hand if needed.

For more information about China Cal's programs, visit their website at www.chinacal.org or contact Mr. Roy Chan at rychan@uci.edu.

Women Undergoing TAVI Using the Medtronic CoreValve® System Have Similar Survival Benefit as Men

Rigorous Trial Design and Monitoring Provides New Insight to Outcomes for Men and Women with Aortic Stenosis

PARIS--(BUSINESS WIRE)--May. 17, 2012-- Medtronic, Inc. (NYSE: MDT) has announced new results from the Medtronic CoreValve ADVANCE Study, which found that women and men benefitted similarly from the Medtronic CoreValve® System. The study, presented at EuroPCR 2012, evaluated patients who were at high-risk for surgical aortic valve replacement. The Medtronic CoreValve System is currently limited to investigational use in the United States.

The gender analysis, a secondary-endpoint evaluation in the real-world CoreValve ADVANCE Study, found that survival rates were nearly identical between genders, with no statistical differences in 30-day and 6-month all-cause mortality, cardiovascular mortality or the 30-day MACCE endpoint (Major Adverse Cardiac & Cerebrovascular Events, a composite of all-cause mortality, myocardial infarction, emergent cardiac surgery or percutaneous re-intervention, and stroke).

Overall, patients experienced low 30-day stroke rates (2.9%), with the combined stroke rates of major and minor strokes being very low (major 1.2%, and minor 1.7%). However, female patients experienced a statistically higher rate of strokes (4.4% vs. 1.4%; p-value <0.01), major vascular complications (14.1% vs. 7.1%; p-value <0.01) and major bleeding (5.0% vs. 3.1%; p-value <0.01). For minor stroke between genders, and for major strokes between genders, differences were not significant, though there was a trend for women to have more minor strokes than men.

"This study is an important contribution to the growing base of research on TAVI, and sheds light on the unique needs for managing severe aortic stenosis in women," said Patrizia Presbitero, MD, Director of Interventional Cardiology at Hospital Humanitas Rozzano in Milan and an investigator in the CoreValve ADVANCE Study, and a professional development co-chair and member of the Leadership Council of WIN (Women in Innovations/ Society for Cardiovascular Angiography and Interventions, SCAI). "We need to know more about gender differences to effectively treat

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patients with heart disease in a more specific way, taking into account those differences that can affect treatment."

Women and men benefited similarly from the CoreValve System even though women (51% of patients) and men (49% of patients) had different risk profiles. Specifically, at the time of enrollment, women as compared to men were:

- Older than males (82.2 years vs. 79.9 years; p-value <0.001);
- Had higher average gradients (47.6 vs. 43.5 mmHg; p-value <0.001) and peak gradients (79.0 vs. 72.5 mmHg; p-value <0.001), a measure of blood flow across the valve;
- Had less coronary artery disease (46% vs. 70%; p-value <0.001); and
- Were prescribed fewer cardiovascular medications, including cholesterol-lowering medications (p-value 0.002) and statins (p-value 0.013).

"The robust ADVANCE trial provides a compelling discovery that the CoreValve System is an excellent therapeutic option for both men and women, and it helps us begin to consider how men and women present differently prior to implant and might be managed accordingly," said Axel Linke, MD, Professor of Medicine at Universitat Leipzig Herzzentrum in Leipzig, Germany and principal investigator of the ADVANCE clinical trial. "An important next step will be to further evaluate why stroke events were more common for women, including the possible role of medications which were prescribed less frequently for women in this study."

The ADVANCE study is one of the largest multicenter transcatheter aortic valve implantation (TAVI) trials to date, with 1,015 patients consecutively treated at 44 experienced TAVI centers in 12 countries. Clinical endpoints were calculated according to Valve Academic Research Consortium (VARC) standardized definitions. All data were independently monitored, all adverse events related to the primary endpoints were adjudicated by an independent Clinical Events Committee (CEC) consisting of experienced cardiac surgeons and interventional cardiologists, and all cerebrovascular events (including stroke and other events) were adjudicated by an independent neurologist using neuroimaging and systematic NIH Stroke Scale assessments.

The Medtronic CoreValve System received CE (Conformite Europeenne) Mark in 2007 for the treatment of patients deemed at high or extreme risk for surgery. Since then, it has been implanted in more than 27,000 people in more than 50 countries outside the US. The CoreValve System is available in three sizes (26mm, 29mm and 31mm), and is the only transcatheter aortic valve implantation system approved for direct aortic or subclavian access. For more information visit Medtronic, Inc. at www.medtronic.com.

Worldwide, approximately 300,000 people have been diagnosed with symptomatic, severe aortic stenosis, and approximately one-third of these patients are deemed at too high a risk for open-heart surgery (D*ecision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? Bernard Iung et al. Eur Heart J (December 2005) 26(24): 2714-2720.*)

Letters to the Editor

Congenital Cardiology Today welcomes and encourages Letters to the Editor. If you have comments or topics you would like to address, please send an email to: LTE@CCT.bz, and let us know if you would like your comment published or not.

Those wishing to have their LTE published will be sent a preproduction draft to review.

New Column Starts Next Month

This special column will be published bimonthly in *Congenital Cardiology Today* with contributors and images from the *Archiving Working Group of the International Society for Nomenclature of Paediatric and Congenital Heart Disease.*

CONGENITAL CARDIOLOGY TODAY

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