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Receptive audience

Developments in stents, CRT find a culture of acceptance in Europe

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MUNICH, Germany – The medical device market in Europe has historically been the backdrop for introduction of the latest new technologies, as well as one of the most important geographic segments of the global market. The cardiovascular device segment in Europe is no exception, often serving as the arena in which new products are first introduced to the global market.

CD&D at the European Society of Cardiology-Congress, Part 1 of 2

The sector is highlighted annually by the congress of the **European Society of Cardiology** (ESC, Sophia Antipolis, France), held here in early September with record attendance. Among the major topics addressed at the congress were new developments in stents and percutaneous intervention, cardiac rhythm therapy, and management of patients with chronic cardiovascular disease.

As shown in **Table 1** on the next page, Europe accounts for a significant proportion of the global burden of cardiovascular disease, with the number of affected individuals in the various cardiovascular disease segments typically exceeding the U.S. Incidence rates for cardiovascular disease in Europe (as indicated by hospital discharge rates for cardiovascular disease) have generally been increasing over the past decade, with a slight decline in the Western European countries more than offset by significant increases in countries in Eastern Europe, including the countries comprising the Commonwealth of Independent States, a group of 12 of the 15 countries of the former USSR.

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Table 1
Worldwide Prevalence of Cardiovascular Disease by Region

Disease Segment	Incidence/Prevalence			
	U.S.	Europe	Japan	Worldwide
Coronary heart disease (CHD)	16 million	18.3 million	5.4 million	63 million
Stroke	5.8 million	6 million	1.8 million	15 million+
Congestive heart failure (CHF)	5.3 million	10 million	—	23 million[1]
Hypertension	73 million	2%-18% (~73 million)	24.7 million	15%-37%
Heart valve disorders	4.6 million	5.9 million[2]	1.9 million[3]	13 million+
Atrial fibrillation	3.3 million	2.3 million[4]	1.3 million	7 million+

[1]developed countries only; [2]estimated from U.S. prevalence based on relative treatment procedure volumes; [3]estimated from U.S. incidence or prevalence based on relative size of population; [4]Western Europe only.

Sources: American Heart Association; British Heart Foundation Health Promotion Research Group; Tatsumi E. et al.; cardiovascular disease prevalence, CHD prevalence and CHD incidence in Europe estimated from ratio of hospital discharges in Europe vs. U.S. based on 2006 Euro Heart Survey data; European Brain Council, CNS Forum, Lundbeck Institute, Nov 2007; New Medicine Inc.; Wilkerson Group; WHO Global Burden of Disease database; Nkomo VT, et al., Lancet 2006; 368:1005-1011; Society of Interventional Radiology; St. Jude Medical; Stuge, O and Liddicoat, J; J Thoracic Cardio Vascular Surgery 2006;132:1258-61; Cardiovascular Devices & Drugs.

Utilization rates for cardiovascular disease therapeutic modalities such as coronary stents and implantable cardiac rhythm management devices are generally lower in Europe than in the U.S., and average selling prices for devices such as drug-eluting coronary stents are also lower, so the cardiovascular device market is smaller in Europe than in the U.S. Nevertheless, Europe represents the second-largest geographic market worldwide, and one that is receptive to new technologies and advanced therapies.

New elements in DES debate

The utilization of drug-eluting stents in Europe, as well as in the U.S., has been a topic of debate since data was presented at the 2006 ESC congress in Barcelona that raised questions about long-term safety of the devices due to an excessive rate of late stent thrombosis. At the 2008 congress, longer-term follow-up data from a number of studies was presented that shows no significant difference in safety between bare metal and drug-eluting stents, and some studies showed a benefit for DES. Ran Kornowski, MD, of **Rabin Medical Center** (Petach Tikva, Israel), described a single-center study comparing DES to bare-metal stents in 4,700 patients treated between April 2004 and June 2007. Of the total, 2,719 patients received drug-eluting stents, and dual anti-platelet therapy was prescribed for three to 12 months. Follow-up ranged from nine months to four years.

Some 71% of the stents used were Cypher stents manufactured by **Cordis/J&J** (Miami Lakes, Florida), 15% were Taxus stents from **Boston Scientific** (Natick, Massachusetts), 11% were Endeavor stents manufactured by **Medtronic** (Minneapolis, Minnesota), and 3% were other types of drug-eluting stents. Drug-eluting stents were shown to be superior to bare-metal stents by all measures analyzed in the study, including target vessel revascularization and MACE, which was 15.8% vs. 23.1% for bare-metal stents.

There was a significant mortality benefit for DES, which was enhanced in diabetic patients. Overall mortality in the study was 35% lower for the DES group. A possible explanation for the mortality difference was the more complete revascularization strategy applied for DES patients. The study had no industry funding.

An extensive analysis of other trials and registries, the latter including data on 80,000 patients with a follow-up of one to four years, comparing DES to bare-metal stents was presented by Patrick Serruys, MD, PhD, of **Erasmus Medical Center** (Rotterdam, the Netherlands) at the ESC congress. The analysis also showed that long-term outcome data demonstrate that drug-eluting stents are equivalent to or better than bare metal stents in essentially all respects, even in STEMI patients for which some cardiologists continue to recommend limited use.

Drug-eluting stents were clearly superior with respect to the need for re-intervention, even for STEMI patients where the probability of re-PCI was 5% for DES compared to 13.5% for BMS. Outcome data from Serruys' own practice in Rotterdam on 7,217 PCI patients at four-year follow-up also favors use of DES in most patient groups. Rates for target vessel revascularization are lower for DES except for treatment of left main disease, bypass grafts, and bifurcations.

A final factor that had initially favored use of bare-metal stents in Europe was cost. In 2001, bare-metal stents cost around €1,400 whereas DES were priced from €1,500 to €2,700. However, as a result of the entry of a number of additional DES suppliers in the market in Europe over the past few years, the price differential has now fallen to below €400 in

almost all countries in Europe, with DES prices now ranging between €800 and €1,000 depending on the country.

The other competing modalities for stents in Europe are bypass surgery and medical therapy. Results from a major study that assessed the safety and efficacy of stents versus bypass surgery, the SYNTAX (SYNergy between percutaneous coronary intervention with a TAXus and cardiac surgery) trial, was presented at the ESC congress by co-principal investigators Serruys and Friedrich Mohr, MD, of the **University of Liepzig** (Leipzig, Germany).

The study was unique in that it included both a randomized arm as well as a registry arm. The patients enrolled in the trial were a high-risk group with three-vessel disease and/or left main disease, a group that historically has been considered primarily candidates for CABG. All patients were initially evaluated jointly by a cardiac surgeon and an interventional cardiologist. If both physicians agreed that the patient could be completely revascularized either with PCI or CABG, the patient was randomized to one of the two procedure arms. Otherwise, patients were entered into a registry and given the treatment recommended by the physician team.

A total of 3,075 patients were included in the study. At 12 months, there was no statistically significant difference in death, stroke and myocardial infarction between the CABG and PCI groups, although the rate for stroke was significantly lower at 0.6% in the PCI group compared to 2.2% in the CABG group. Overall MACE rates, however, favored the CABG group, primarily because of a significantly lower rate of revascularization in that group of 5.9% versus 13.7% for the PCI group.

Although the trial showed that PCI is inferior to CABG in patients with complex lesions, the only adverse consequence of undergoing PCI is a higher risk of a repeat procedure. Conversely, patients who opt for CABG are at higher risk for stroke, mainly because they typically must wait longer before undergoing their procedure. Mohr noted that the revascularization rates for PCI and CABG have been trending closer for the past three decades, with the difference dropping from about 30% in the 1980s to 17% in the late 1990s and now to 7% in the late 2000s. The gap is likely to narrow further in the future, due to continued improvements in PCI techniques and, perhaps most importantly, advances in adjunctive therapy.

A similar outcome was reported for use of drug-eluting stents vs. CABG in diabetic patients in the CARDia (Coronary Artery Revascularization in Diabetes) trial. The trial included 510 diabetic patients with multi-vessel disease enrolled at 24 centers in the UK and Ireland who were treated either with CABG or PCI. Some 71% of the PCI procedures employed Cordis Cypher stents.

As in the SYNTAX trial, there was no significant difference between the two treatment groups except for a higher (7.3%) rate of revascularization in the PCI group compared to 2% in the CABG group. The study was not conclusive because enrollment did not reach the prescribed goal, making the trial's statistical power inadequate. Akhil Kapur, MD, of **London Chest Hospital**, nevertheless stated in an ESC press conference that the results show that PCI may be considered a reasonable strategy in diabetic patients with multi-vessel disease. The results were significantly better than for the previous BARI trial, which was the last to assess PCI vs. CABG in diabetic patients according to Kapur, probably because of improvements in adjunctive therapy.

Summarizing the latest results of clinical studies of drug-eluting stents at an ESC press conference, Carlos Di Mario, MD, of **Royal Brompton Hospital** (London), concluded that there is no difference in safety, as measured by rates of death and myocardial infarction, between DES and bare metal stents. The most probable explanation is that, while there is an excess of late stent thrombosis events with DES which in more than two-thirds of cases are associated with death or MI, there is an equal and offsetting incidence of events associated with the higher rates of restenosis and reintervention with bare metal stents.

As shown in **Table 2**, cardiologists in Europe reacted to the safety issues raised for drug-eluting stents in September 2007 by reducing their utilization of the devices. Since about 1 million PCI procedures are performed in Europe annually, 80% of which use stents, the data in Table 2 on DES utilization indicates that the number of drug-eluting stents implanted annually in Europe dropped by about 28,000 from late 2005/early 2006 to mid-2007.

Utilization rates for DES are believed to have remained relatively constant over the past year in Europe, but may begin to increase now that there is evidence that safety is not compromised compared to bare metal stents, particularly in light of the significant drop in prices for DES. Likewise, the market for

Table 2
Drug-Eluting Coronary Stent Market Penetration in Europe

Time Period	Market Penetration in Europe
2Q02	2%
2Q03	13%
2Q04	28%
2Q05	45.4%
2Q06	54.5%
2Q07	51%

Sources: Boston Scientific; E. Camenzind, presented at the 2006 World Congress of Cardiology.

drug-eluting stents may begin to grow, albeit slowly, as prices stabilize and utilization begins to expand. The global DES market dropped from $5.4 billion to $4 billion between 2006 and 2007, a 26% decline.

Next-generation stents show promise

Although drug-eluting stents appear to have earned a reprieve with respect to safety, manufacturers are keenly aware that reduction of late thrombosis, as well as of hypersensitivity reactions reported with first-generation DES, is a high priority for the next generation of devices. As discussed by Renu Virmani, MD, of **CVPath** (Gaithersburg, Maryland), at a satellite symposium held prior to the ESC congress, there is evidence for persistence of fibrin out to 18 months in first-generation DES, specifically the Cypher stent from Cordis and the Taxus stent from Boston Scientific, as well as incomplete endothelialization for both devices. Furthermore, in patients who experience stent thrombosis, there are more uncovered stent struts.

Virmani suggested that late thrombosis may be a problem in myocardial infarction patients who have been treated with DES, since such patients typically have some thrombus already present when the stent is implanted, which could further exacerbate malapposition of the stent and lead to thrombosis.

However, with next-generation stents such as the Xience V everolimus-eluting stent from **Abbott Vascular** (Abbott Park, Illinois) and the Endeavor from Medtronic, endothelial coverage of the stent is significantly improved, at least in animal studies. In addition, the level of inflammation of the vessel wall for Xience V is only one-third that for Cypher at long-term follow-up, and inflammatory reactions, possibly due to the nature of the drug-eluting polymers used in first-generation DES, are believed to play a role in late stent thrombosis.

Other characteristics of second-generation stents such as Xience V include a lower dose of anti-restenosis drug (88 ug vs. 150 ug for Cypher), resulting in a reduced retardation of endothelial tissue growth; and complete release of the drug over a period of 120 days. Virmani also has found that expression of molecular markers related to lack of endothelial cell proliferation is lower for Xience V compared to Cypher and Taxus. She concluded that the evidence to date indicates that second-generation drug-eluting stents such as Xience V should be safer and more biocompatible than first-generation devices.

Eberhard Grube, MD, of **HELIOS Heart Center** (Siegburg, Germany), discussed the latest results of the SPIRIT V registry of patients receiving the Xience V stent. 2,700 patients are included in the registry, of which 2,663 have been analyzed by Grube. SPIRIT V represents real-world experience with the Xience V, since most patients have high complexity lesions (82% are Type B2 or C) and a high percentage (30%) are diabetic.

Initial 30-day results from the registry show a low rate of target lesion revascularization of 0.1% (0.3% on an intent-to-treat basis), and low rates of acute and subacute thrombosis (0.15% and 0.26% respectively). The MACE rate for the study was 2.6%, and procedural success was 98%. Grube said the results confirm the ease of use of the Xience V, as well as safety and efficacy, at least in the short term.

Neville Kukreja, MD, of **Erasmus Medical Center** (Rotterdam, the Netherlands), discussed the results of the X-SEARCH registry at the ESC satellite symposium, which includes 649 patients treated with the Xience V in Rotterdam. At six month follow-up, the target vessel revascularization rate was 3.1%.

The patients represented real-world experience, since 90% had Type B2 or C lesions, and 39% were STEMI patients. The results were compared with previous Rotterdam registry data for the Cypher and Taxus stents, and no significant differences were observed in safety or efficacy, although Kukreja said the Xience V may be a more effective stent than Taxus.

Results from the LEADERS (Limus Eluted from a Durable vs. Erodable stent coating) trial, which is evaluating the Biomatrix Flex coronary drug-eluting stent from **Biosensors International** (Singapore), were discussed at the ESC congress by Stephan Windecker, MD, of **Bern University Hospital** (Bern, Switzerland). The Biomatrix Flex incorporates a bioabsorbable polymer applied only to the abluminal surface of the stent and loaded with biolimus A9, a drug that has similar properties to sirolimus used in the Cypher stent.

The trial assessed performance of the Biomatrix Flex stent versus the Cypher stent in 1,707 patients. At nine-month follow-up, composite death, MI and target vessel revascularization was 10.5% for Cypher vs. 9.2% for Biomatrix. In-stent stenosis was lower for the Biomatrix stent at 20.9% compared to 23.3% for Cypher. The study demonstrated that the Biomatrix stent is non-inferior to Cypher from both a clinical and an angiographic perspective. The bioabsorbable polymer coating may help reduce inflammation in the vessel wall as is observed with durable polymer coatings, but longer-term data will be needed to evaluate its effect on late stent thrombosis.

Serruys described results of initial studies with one of the first third-generation drug-eluting stents, a bioabsorbable everolimus-eluting stent under development by Abbott Vascular. Bioabsorbable stents can potentially provide some significant advantages over today's permanent metal implants, such as reduction in the time period for which dual anti-platelet therapy is needed, elimination of late stent thrombosis, facilitation of treatment of in-stent restenosis, and avoidance of long-term blockage of side branch ves-

sels. In addition, bioabsorbable stents could help to preserve bypass surgery as a future treatment option in patients who receive multiple stents, and would avoid the interference with CT and MR imaging procedures created by existing metal stents.

Bioabsorbable stents could be particularly valuable for applications in the peripheral arteries, where strut fracture has continued to plague use of metal stents, as well as in pediatric applications where the use of metal stents is problematic because they fail to grow along with the artery. However, cardiologists do not want to compromise on radial strength and vessel support with a bioabsorbable stent, and also want deliverability and ease of use to be equivalent to metal stents.

Efforts to develop bioabsorbable stents have so far met with limited success mainly because the stent fails to provide adequate support for the vessel over an adequate period of time, as exemplified by the first version of the Absorbable Metal Stent (AMS) from **Biotronik** (Berlin, Germany). Biotronik is now developing a new version that will offer a slower biodegradation profile.

A second company developing a bioresorbable coronary stent, **REVA Medical** (San Diego), commenced first-in-man trials in June 2007 (the RESORB trial). The REVA stent is comprised of a tyrosine-derived polycarbonate material that has strength, flexibility, recoil and X-ray visibility equivalent to that of metal. A paclitaxel-eluting version is also in development. REVA has established a broad strategic relationship with Boston Scientific.

The Abbott Vascular bioabsorbable stent is constructed of poly-L-lactide and elutes the anti-restenosis drug everolimus. The latest version of the Abbott stent is now being evaluated in the ABSORB trial. Six-month results from the trial, which has enrolled a total of 30 patients, were published in *The Lancet* in March. As described by Serruys, late loss at six months for the Abbott bioabsorbable stent based on IVUS and angiographic analysis of 24 patients is 0.44 mm, intermediate between that for the Xience V of 0.1 mm and the Abbott ML Vision bare metal stent of 0.87 mm.

The reported MACE rate at six months and at one year was 3.4%, and no subacute or late stent thrombosis has been observed. The neointimal hyperplasia area for the bioabsorbable stent at six months was 0.5 mm^2 compared to 0.3 mm^2 for the Xience V, indicating that the device is effective in inhibiting neointimal tissue growth. The latest data from the ABSORB trial, as discussed by Serruys at the ESC congress, shows evidence for absorption of the stent via IVUS as well as OCT, with disappearance of structures related to the struts, and all stents have remained patent at two years.

Importantly, there is evidence for restoration of vasomotion in the stented region, and the vessels respond to administration of vasodilating drugs. No inflammation is evident in the stented region at two-year follow-up, and there is evidence for coverage of the necrotic core with endothelial tissue and in one case a reduction in size of the core. Serruys said he expects pivotal trials with the Abbott bioabsorbable stent to be complete by 2010.

Another new development in percutaneous intervention described at the ESC congress may improve procedural outcomes particularly for patients having complex lesions. As discussed by Alexander Ijsselmuiden, MD, PhD, of **OLVG Hospital** (Amsterdam, the Netherlands), in a symposium on emerging technologies in stenting, use of magnetic guidance of PCI procedures with the Niobe Magnetic Navigation System from **Stereotaxis** (St. Louis) results in a significant reduction in procedure time, facilitates treatment of complex lesions, results in less entry of side branches, and a lower rate of vessel perforation. The system uses two 0.8 Tesla magnets controlled by computer software to remotely manipulate the tip of an interventional guidewire.

The guidewire used in the study was the Titan, a conventional guidewire with a 2 mm-3 mm magnet attached to the tip, also from Stereotaxis. In a randomized trial conducted from January through May 2007, results from 47 procedures performed with the Niobe system were compared to 45 procedures performed using conventional manual guidance. In spite of the presence of more complex lesions in the magnetic guidance group, there was no difference in procedural success rate and procedure time was significantly reduced, from 41 to 30 minutes, with the use of magnetic guidance. Fluoroscopy time was reduced to less than half (7.5 vs. 16.1 minutes), and the use of contrast was reduced from 180 to 122 ml, resulting in an improvement in safety for magnetic guidance.

Cost is the primary drawback of magnetic guidance, since the price of the Niobe system is €1.4 million. However, the shorter procedure time and reduced use of contrast results in a reduction in cost excluding the cost of the magnetic guidance system. Ijsselmuiden said that 1,000 patients would need to be treated to offset the cost of purchase of the guidance system, so it may prove cost-effective in high-volume centers. Patients with Type C lesions were the most likely to benefit from magnetic guidance due to a reduction in perforations, reduced radiation exposure, and lower use of contrast agents.

A separate study using the Niobe system at three centers in Germany, discussed by Rudiger Blindt, MD, of **University Hospital Aachen** in Germany, at an ESC press conference reached similar conclusions, and found that some lesions which could not be treated with conventional PCI could be treated when magnetic guidance was employed.

Table 3
Comparison of Global Utilization of Cardiac Rhythm Therapy

Region	High-Power CRT Implants per Million Inhabitants	Low-Power CRT Implants per Million Inhabitants
U.S.	600	941
Western Europe	189	905
Japan	40	394
China	<1	24

Source: Medtronic

The use of embolic protection devices to improve PCI outcomes in the treatment of saphenous vein grafts was addressed in the AMEthyst study, discussed by Srihari Naidu, MD, of **Winthrop University Hospital** (Mineola, New York). The AMEthyst trial evaluated 800 patients and compared the Interceptor Plus embolic protection device from Medtronic to the Medtronic Guardwire and the Boston Scientific FilterWire.

While the Interceptor Plus produced an equivalent rate of MACE (8% vs. 7% for controls), Naidu said that the results demonstrate the need for improved protection devices, since the MACE rate remains high compared to that for interventions in other lesion types. At present, according to Naidu, embolic protection devices are used in only 25% to 30% of saphenous vein graft interventions, and the average MACE rate overall is 7.8%.

Evolving role for CRT in Europe

Cardiac rhythm therapy, and in particular its role in heart failure treatment, was another important topic at the ESC congress. The global market for cardiac rhythm therapy devices reached $10 billion in 2007, an increase of 5% over 2006. As shown in **Table 3**, CRT for low-power rhythm control devices such as pacemakers is utilized more widely in Western Europe than in the U.S., whereas high-power CRT device therapy is much less widely used in Europe compared to the U.S.

Considerable effort is being devoted to improving patient selection for CRT. In Germany, although 25,000 ICDs are implanted every year at a cost of €40,000 each, there are still 100,000 sudden cardiac deaths annually, indicating that not all patients who could benefit from an ICD are receiving one. In addition, a number of patients who have implants never receive a shock, so there is a significant waste of health care resources due to the inability to accurately identify those individuals who will benefit. A number of non-invasive imaging techniques are being evaluated, mostly based on ultrasound, to improve the ability to select patients for ICD implants.

Another approach was described at the ESC congress by **BMDSys** (Jena, Germany) which involves non-invasive mapping of the heart's electrical impulses to detect patterns associated with an underlying heart rhythm disorder. The company's Apollo CXS system is unique in that it uses highly sensitive superconducting magnetic field detectors to measure the patterns generated by the heart's electrical activity. An array of 55 detectors allows 3-D mapping of the complete heart in two minutes. The system analyzes fragmentation in the heart waveforms which is indicative of a rhythm disturbance.

Unlike ECG monitoring methods used to detect arrhythmias, the BMDSys technology does not need to capture an arrhythmia event in order to make a diagnosis. The system can be used both for static testing as well as stress testing. BMDSys has just introduced the Apollo CXS in Europe, with one system already placed and a second placement in progress. The Apollo CXS is priced at approximately €1 million, similar to the price of an MRI scanner. Reimbursement for the magnetic field imaging (MFI) exam has not yet been established in Europe, but will probably be around €250. The company has estimated that each instrument placed in Germany could produce €1.3 million in healthcare cost savings.

New cardiac rhythm therapy devices were introduced at the ESC congress by Boston Scientific and Medtronic. Boston Scientific introduced the Cognis CRT-D and Teligen ICD, both of which provide high energy as well as increased longevity. Battery life has been extended to seven to eight years, while pulse energy has been increased to 41 joules. The new battery employed in the devices combines technology used previously in Boston Scientific's pacing and ICD implants.

Medtronic introduced the EnRhythm MRI SureScan pacemaker, which is pending CE mark approval. The EnRhythm is an MRI-safe device, and will enable the growing number of individuals with pacemaker implants to undergo MRI scans without risking damage to their device. Other pacemakers are subject to extensive vibration when exposed to the magnetic fields typically encountered in an MRI scanner, which can easily damage device components.

Medtronic estimates that 50% to 75% of all patients with pacemakers will be denied an MRI scan during their lifetime due to the incompatibility of current-generation pacemakers with MR scanners. About 1 million patients receive pacemaker implants worldwide each year. Medtronic began a clinical trial to obtain FDA approval of the EnRhythm MRI SureScan.

A new development in cardiac ablation was described by Luc Jordaens, MD, of Erasmus Medical Center. Jordaens has evaluated the use of robotic navigation systems in electrophysiology to improve the

guidance of catheter ablation procedures in the heart. With existing ablation techniques, success rates are quite low, at 50% for ablation of atrial fibrillation. Complication rates range from 1.5% to 5.1%, a significant issue since procedures are often performed in younger, healthy patients.

Jordaens has assessed two different technologies for their ability to improve the effectiveness and safety of catheter ablation, the Sensei robotic catheter manipulation system from **Hansen Medical** (Mountain View, California) and the Niobe magnetic catheter guidance system from Stereotaxis. The Sensei system, while able to guide transseptal puncture and access to the pulmonary veins, does not reduce the force applied by the catheter to the heart tissue compared to conventional catheter ablation. As a result, two of 40 patients treated by Jordaens using robotic navigation had pericardial tamponade.

In contrast, the Niobe systems' magnetically guided catheters are much less stiff, and create less trauma, since forces applied to the heart tissue are dramatically reduced. In addition, the ablation lesions created via magnetic guidance are much cleaner and more precise. Jordaens has found that ablation can be performed even during arrhythmia. The system also enables automatic mapping of the ablation pattern, and allows procedures to be streamlined, reducing cath lab time and radiation exposure.

The greater stability of the catheter tip that can be achieved with magnetic guidance may give more durable ablations, according to Jordaens. To further improve the efficacy of catheter ablation, Jordaens has switched from electrical ablation to cryoablation. Cryoablation devices, such as the Freezor and Arctic Front catheters available from **CryoCath Technologies** (Montreal), are increasingly becoming the preferred modality for ablation to treat cardiac arrhythmia in Europe.

TomTec workstation creates novel views for cardiac imaging

By JOHN BROSKY
***CD&D* European Editor**

The company that brought the world 3-D echocardiography (3-D echo), **TomTec** (Unterschleissheim, Germany), is returning to its roots to refresh the picture in cardiac magnetic resonance imaging (MRI). At last month's **European Society of Cardiology** (ESC; Sophia Antipolis, France) congress in Munich, Germany, TomTec was showing CardioArena, a multi-modality imaging workstation preannounced in March, that featured the soon-to-be-famous "beutel."

Also called the "dancing bag," the green 3-D rendering on the CardioArena screen is actually the left ventricle of a patient shown in a view as intuitively friendly as the pictures in an anatomy book rather than the familiar but disorienting black-and-white 2-D images produced by MRI. "Beutel" is the German word for "bag" and in a moment of national pride, TomTec trademarked the word for cardiac imaging. "Dancing bag" is far more catchy for radiology staff, while cardiologists are quite likely to call it the left ventricle.

Already used in reconstructions of temporal 3-D echo, also called 4-D echo because the dimension of time is added, the beutel representation combined with MRI allows the cardiologist to click on slice views to zoom in on suspect areas of the ventricle.

As a result, a consultation can be conducted simultaneously with reference to echo and MRI images on the same screen with intuitive navigation.

CardioArena is the only platform capable combining 2-D, 3-D and 4-D imaging data from three modalities – ultrasound, MRI and the cath lab – and it is vendor-independent. CardioArena also connects with the hospital information system, the picture archiving and communication system (PACS) and is accessible over CardioArena Web for anytime/anywhere consultations by referring physicians, surgeons or satellite hospitals.

"Some cardiologists are echo-oriented while some have a preference for MRI, and those orientations affect their perceptions," said Bernard Mumm, president/chief technology officer of TomTec. "There is a difference in quantification for each modality and they can show different results with echo saying everything is all right and MRI showing things are not good," he said.

"Up to now, if you looked at the left ventricle it is always in 2-D and cardiologists need to do a mental reconstruction," Mumm said, adding that studies

showed their mental reconstructions are less-than-perfect.

The other problem for clinicians is that a single patient may undergo imaging in different modalities and these images are locked in silos, such that the consulting cardiologist needs to visit multiple silos or even physical sites to view diagnostic images of the same patient. "What we have done is combine all modalities on one platform and can show it to them in temporal 3-D," said Mumm. A CT-enhanced prototype for CardioArena is now in development, "but it is not yet ready to talk about as a product," he said.

TomTec's approach to imaging for radiology, cardiology and ob/gyn is mathematical and not visual reducing modalities to common quantification methods and then specializing in the algorithms to render a single view in 3-D with the capability now to switch between modalities.

The company generates only 20% of its revenues from direct sales of branded products such as CardioArena. The remaining 80% is generated through licensing of its modules and algorithms to original equipment manufacturers (OEMs) such as **Philips** (Eindhoven, the Netherlands), **Toshiba** (Tokyo), or in ophthalmology, **Carl Zeiss** (Jena, Germany), which is developing images of the retina acquired by optical coherence tomography (OCT) and processed using Tomtec technology. **Siemens** (Erlangen, Germany) offers TomTec ultrasound workstations directly on its website.

Mumm said among TomTec's OEM customers, some can be competitors, but most are partners. "We bring them a module, show that it is both CE-marked and FDA-approved, which makes it easy for them to include the module in their applications," he said.

At ESC, TomTec unveiled the 2-D Cardiac Performance Analysis, a new product feature for the new CardioArena. A speckle tracking analysis tool that can analyze 2-D data from a range of ultrasound machines from different vendors, the 2-D cardiac performance package enables quantitative assessment of displacement, velocity and strain in individual muscle segments.

This analysis aids in the diagnosis of pathologies such as hypertrophic cardiomyopathy or dyssynchronous ventricles, which may need to be treated by cardiac resynchronization therapy.

TomTec began with a management buyout from **Kontron** (Plaisir, France) in 1990 by a group of executives who had developed 3-D MRI imaging. The company made waves when this team applied its know-how to ultrasound and introduced the world's first 3-D imaging capable of transforming the grainy black-and-white images into intuitive, anatomical renderings.

TomTec remains privately held, with employees holding the majority of shares, and does not report revenues.

Pharma developments

New studies on drug therapies are presented at ESC

By DON LONG
***CD&D* National Editor**
and Staff Reports

While this month's lead story from the **European Society of Cardiology** (Sophia Antipolis, France) annual congress focuses on developments in device therapies and radiology, the conference also provided an overview of some of the latest research in pharmaceutical interventions for cardiovascular care.

Following is a summary of the key reports:

* A report on Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study concluded that intensive LDL-cholesterol lowering with the combination of simvastatin and ezetimibe in patients with mild to moderate aortic stenosis appears to reduce the risk of coronary artery disease events (as has been shown in previous trials), but not the rate of progression of aortic valve disease. The use of simvastatin and ezetimibe in such patients was generally well tolerated and safe.

SEAS investigated the effects of intensive cholesterol lowering with the combination of simvastatin (40 mg daily) and ezetimibe (10 mg daily) in patients with aortic stenosis, common among older people in Western populations. Left untreated, it can progress to death from heart failure or cardiac arrest.

Compared with placebo, the combination of simvastatin and ezetimibe reduced LDL-cholesterol (the primary endpoint) by an average of 61%, corresponding to a reduction of about 2 mmol/L (76 mg/dl). The combination of simvastatin and ezetimibe did, however, produce a statistically significant 22% proportional reduction in the secondary endpoint of atherosclerotic events alone: 148 (15.7%) in the simvastatin plus ezetimibe group versus 187 (20.1%) in the placebo group.

The study was initiated and designed by academic researchers in Scandinavia, and carried out at 173 clinical centers in Norway, Denmark, Sweden, Finland, Germany, UK and Ireland.

• A report was presented on the DECREASE III Study, conducted in the Netherlands between June 2004 and April 2008, concluding that patients treated with Fluvastatin, a product from **Novartis** (Basel, Switzerland), showed an improved cardiac outcome after surgery.

In the study, 497 statin-naive patients scheduled for vascular surgery were included in the trial at **Erasmus MC** (Rotterdam, the Netherlands). Patients were randomized to receive either placebo or fluvastatin extended release, 80 mg, once daily. Treatment was started at the outpatient clinic on the day of randomization, median 37 days prior to surgery and was continued during the first 30 days after surgery. Inflammatory markers at baseline, including hs-CRP and IL-6 were assessed in patients allocated to fluvastatin or placebo.

At hospital admission, levels of hs-CRP and IL-6 were significantly lower in patients on fluvastatin. The primary analysis was intention-to-treat and involved all patients who were randomly assigned to either fluvastatin or placebo.

Directly after surgery, study treatment was temporarily discontinued in about one-third of patients for a variety of reasons.

Myocardial ischemia (the primary endpoint) was detected in 74 (14.9%) patients within 30 days of the initial vascular surgical procedure. A total of 27/250 (10.9%) patients allocated to fluvastatin reached the primary endpoint compared to 47/247 (18.9%) patients allocated to placebo treatment (OR 0.53; 95% CI 0.32-0.88). Hence, the number needed to treat (NNT) to prevent one patient experiencing myocardial ischemia was 12.5 patients.

A total of 18 (3.6%) patients died within 30 days after surgery (the secondary endpoint) of which 12 (2.4%) were attributable to cardiovascular causes. Additionally, 25 (5.0%) patients experienced a nonfatal myocardial infarction within 30 days after surgery. The combined endpoint of cardiovascular death and nonfatal myocardial infarction was reached in 37/497 (7.4%) patients.

A total of 12/250 (4.8%) patients allocated to fluvastatin therapy reached the combined endpoint, compared to 25/247 (10.1%) allocated to placebo. Hence, fluvastatin therapy was associated with a 52% relative reduction in the incidence of MI (OR 0.48; 95% CI 0.24-0.95). The NNT for the composite endpoint of cardiovascular death or nonfatal MI is 18.9 patients.

• The management of acute coronary syndromes requires the use of anticoagulants, antiplatelet agents (aspirin, clopidogrel and/or glycoprotein [GP] IIb/IIIa inhibitors), beta-blockers, thrombolytics in some cases, and revascularization/reperfusion. In all, bleeding and possibly also blood transfusion have emerged as major contributors to worse outcome in patients with acute coronary syndrome.

A study presented at the conference underlined the need for the appropriate selection of drugs, drug

doses and arterial approaches, combined with systematic evaluation of the bleeding risk prior to starting therapy to help prevent bleeding and improve patient outcome.

A past history of bleeding, the presence of renal failure, the use of an early invasive approach, excess dose of antithrombotic agents, and use of GP IIb/IIIa inhibitors have also been identified as strong predictors of the risk of bleeding. Conversely, careful selection of drugs, giving precedence to drugs with less potential for bleeding, use of a radial vs. femoral approach for invasive strategy, and systematic use of proton pump inhibitors to avoid gastro-intestinal bleeding during the initial phase, are all measures that have the potential to reduce the bleeding risk.

The study concluded that more consistent inhibition of platelet aggregation leads to better clinical outcome, albeit with an increased risk of bleeding.

• Since rofecoxib (Vioxx) was withdrawn from the worldwide market based on the safety findings of the Adenomatous Polyp Prevention on Vioxx (APPROVe) study, the uncertainty around the cardiovascular safety of NSAIDs and COX-2 inhibitors remains and leaves practitioners with difficult decisions for the hundreds of millions of patients worldwide who continue to require pain-relieving therapy to maintain an acceptable quality of life.

A report summarized the goal of the Prospective Radomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen and Naproxen (PRECISION), now underway, addressing the cardiovascular risks of anti-inflammatory drugs used to treat arthritis, involving 2,000 patients. Questions concerning anti-inflammatory drugs, the PRECISION – Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen and Naproxen – trial in more than 20,000 patients with osteoarthritis is now under way.

Importantly, the FDA recently summarized a statement that in various controlled clinical trials the cardiovascular risks of COX-2 selective drugs have been indistinguishable from non-selective NSAIDs, thus also raising serious questions about the safety of the latter. As such, the FDA mandated a "boxed warning" for COX-2 selective inhibitors and traditional NSAIDs alike in view of the potential of these agents to increase adverse cardiovascular outcomes. Unfortunately, none of the reported randomized trials undertaken with NSAIDs and COX-2 selective inhibitors have thus far been specifically designed to examine cardiovascular outcomes. Thus, the current situation is one of classic "equipoise." Adequately powered, independently run randomized clinical trials prospectively designed to capture cardiovascular outcomes are urgently needed.

The report said that until trials such as PRECISION are completed, careful risk/benefit analysis needs to be undertaken for all anti-inflammatory agents regarding their potential cardiovascular risk, hypertension and its clinical sequels.

• **GlaxoSmithKline** (GSK; London) reported that the results of the Integrated Biomarkers and Imaging Study-2 (IBIS-2) showed that use of the selective Lp-PLA2 (lipoprotein-associated phospholipase A2) inhibitor, darapladib, in addition to standard of care treatment, prevented expansion of the necrotic core, a region within coronary plaque associated with a high risk of rupture.

Preventing expansion of the necrotic core may reduce the risk of recurrent heart attacks in patients with coronary heart disease (CHD), according to GSK. Although the differences between treatment groups in the primary endpoints of plaque deformability or reduction of the inflammatory biomarker hsCRP were not significant, darapladib significantly reduced activity of the enzyme Lp-PLA2. Numerous studies suggest that high levels of Lp-PLA2 are predictive of coronary heart disease.

The Phase II exploratory IBIS-2 trial showed: that the co-primary endpoints of plaque deformability and plasma levels of hsCRP, showed no significant differences between darapladib and placebo treatment groups, but trended positively; and key secondary endpoints showed significant effects of darapladib on plaque composition and plasma levels of Lp-PLA2 activity.

On average, after 12 months, patients treated with placebo experienced a significant increase in necrotic core volume while expansion of the necrotic core was halted in the darapladib-treated group. This resulted in a significant treatment difference in favor of darapladib. The effect of darapladib on necrotic core was consistent among several subgroups. The activity of circulating Lp-PLA2 was reduced by 59% over placebo. Patients received recommended standard of care, including antiplatelet agents (99%) and statins (90%).

Overall, darapladib was well tolerated with no major safety concerns observed. The incidence of adverse events leading to withdrawal was similar with 7% (n=11) in placebo and 4% (n=7) in the darapladib group. There were no differences in the composite of CV death, MI, stroke and coronary revascularization. Lp-PLA2 is an enzyme found in blood and atherosclerotic plaque. Enhanced Lp-PLA2 activity has been implicated in the development and progression of atherosclerosis and large amounts of Lp-PLA2 are present in the necrotic core of rupture-prone human coronary plaques.

• **Medicure** (Winnipeg, Manitoba) said at the meeting that data from a 263-patient trial of Aggrastate (tirofiban HCL) showed that the drug significantly lowered the incidence of heart attack after elective coronary angioplasty in coronary artery disease patients who have shown poor response to standard oral antiplatelet agents, aspirin and clopidogrel.

Results of the study, designated 3T/2R (Tailoring Treatment with Tirofiban in patients showing Resistance to aspirin and/or Resistance to clopidogrel), demonstrated proof of concept, with 20.4% of patients in the Aggrastate group showing periprocedural myocardial infarction – defined as the elevation of Troponin I or T at least three times the upper limit of normal within 48 hours after the procedure – vs. 35.1% of patients in the placebo group.

CVT opens first FGF-1 site

CardioVascular BioTherapeutics (CVBT; Las Vegas) reported the opening of its first U.S. site for patient enrollment for its Phase II clinical trial for the treatment of severe coronary heart disease. In the coming weeks, CVBT said it will announce additional sites as they open for enrollment. In the Phase II trial, CVBT's drug candidate containing human fibroblast growth factor-1 (FGF-1) will be injected into patients' hearts, stimulating angiogenesis. The drug will be delivered using the NOGA XP Cardiac Navigation system and the MyoStar injection catheter.

Subjects will be between 25 and 75 years of age with at least a three month history of chronic stable angina triggered by physical exertion and must have a **Canadian Cardiovascular Society** anginal classification III or IV while receiving optimal medical therapy. Their treating cardiologist will have determined that they are generally not suitable for interventional therapy or bypass surgery.

"Developing a clinical trial protocol such as ours takes an extraordinary amount of time and effort, and I am pleased to finally open our Phase II heart trial for patient screening," said Daniel Montano, president/CEO of CVBT. "I expect additional investigators at other hospitals to begin screening patients in the coming weeks. Our target is 30 hospitals for this international Phase II heart trial."

CVBT is developing human FGF-1 for cardiovascular diseases characterized by inadequate blood flow to a tissue or organ. In addition to the Phase II trial it is conducting in patients with severe coronary heart disease, the company has two FDA-authorized clinical trials in the areas of impaired wound healing seen in diabetics and in patients suffering from peripheral artery disease of the legs. An additional study is being conducted in patients with chronic back pain who may have perfusion defects to their spine.

In brief . . .

• **Cytokinetics** (South San Francisco, California) said it began its third Phase IIq trial of CK-1827452, a cardiac myosin activator in development for acutely decompensated or chronic heart failure. The study will test an intravenous formulation of the drug in patients with stable heart failure undergoing clinically indicated coronary angiography in the cardiac catheterization laboratory. The primary objet is to measure the potential effects of the drug on myocardial efficiency, defined as the ratio of ventricular performance to myocardial oxygen consumption. Secondary objectives include ventricular performance, myocardial oxygen consumption, hyemodynamics, pressure-volume relationships and systolic ejection time. CK-1827452 is partnered with **Amgen** (Thousand Oaks, California).

• **Diffusion Pharmaceuticals** (Charlottesville, Virginia) initiated a Phase I/II trial of lead product trans-sodium crocetinate (TSC) for intermittent claudication (severe leg pain) associated with peripheral artery disease. Data from the randomized, double-blind, placebo-controlled, doses-ranging study are expected in early 2010. Primary endpoints are peak walking time and claudication onset time. TSC is a small molecule intended to enhance diffusion of oxygen through blood plasma to treat hypoxia and related conditions.

• **GTC Biotherapeutics** (Framingham, Massachusetts) reported that the FDA assigned priority review to its biologics license application for ATryn 9recombinant human antithrombin) in the treatment of patients with hereditary antithrombin deficiency at risk of deep vein thrombosis and other thromboembollisms following surgery. The FDA's action date is Feb. 7, 2009. GTC signed a U.S. marketing deal for ATryn with **Ovation Pharmaceuticals** (Deerfield, Illinois) in June.

Personnel File

• **Neovasc** (Vancouver, British Columbia) reported appointments to new marketing and sales positions. Cynthia Roney was named VP of marketing and Sean Moore VP of sales. Roney was president/CEO of Xillix Technologies, which was acquired by Novadaq Technologies, while Moore was director of sales at Medical Ventures. Neovasc is comprised of the former Medical Ventures, Neovasc Medical Ltd. and B-Balloon Ltd.

• René Spaargaren, MD, has been named chief medical officer of **Stentys** (Paris). Previously, he was VP of international clinical affairs at ev3. Stentys is making a drug-eluting stent for treatment of blocked coronary artery bifurcations so that patients might avoid open-chest surgery.

• **Tryton Medical** (Research Triangle Park, North Carolina) has named Brett Farabaugh CFO and Douglas Ferguson VP of regulatory & clinical. Farabaugh was CFO for StrikeIron, while Ferguson has more than 18 years of experience in regulatory and clinical affairs. Tryton Medical makes stent systems.

International Report

Stem cell secretions may improve outcomes for MI patients

A *CD&D* Staff Report

There may be a new way to improve survival and recovery rate after a heart attack, according to a report in the June issue of *Stem Cell Research* by scientists at the **Institute of Medical Biology** (IMB; Singapore) and Bioprocessing Technology Institute (BTI; also Singapore) and **University Medical Center Utrecht** in the Netherlands. The method, developed in laboratory research with pigs, is the first non-cell based therapeutic application of human embryonic stem cells, according to the scientists. It entails using secretions from stem cells.

In their studies with pigs, the researchers found that the administration of secretion from stem cells minimized heart injury by enhancing reperfusion therapy (angioplasty and cardiac bypass surgery) and reducing tissue death by another 60%. Heart function was also markedly improved, the scientists report in the paper.

By demonstrating the efficacy of this secretion in an experimental pig model, currently the best approximation to a human heart attack patient undergoing reperfusion therapy, the researchers say that they have addressed the longstanding problem of reperfusion injury in the most clinically relevant experimental setting.

"Using secretion instead of cells allows us to circumvent many highly intractable problems such as tumor formation, immune compatibility, cell viability, delivery, costs and timeliness," said IMB's Dr Lim Sai Kiang, who leads the collaboration.

Unlike the more common approach of directly administering stem cells for therapy, this new method carries negligible risk of tumor formation or rejection by the body, according to the report. In the pig research model, this approach minimized heart injury after a heart attack. The research was carried out on pigs because it is the closest animal approximation to the human heart in terms of size, structure and function, the researchers noted.

The scientists say the findings are important because they show that the new method can overcome the unwanted side effects of reperfusion, currently the best therapeutic option available to heart attack patients. Reperfusion is the restoration of blood flow to the oxygen-deprived heart after a heart attack.

"This is a major discovery of clinical significance. There are some problems and issues associated with the use of stem cells to treat heart attacks and blocked arteries in the heart, and with this new method, many of these issues are removed. Potentially, we may have an important way to treat heart attacks. More tests will need to be done and human trials planned," said advisor to the Singapore researchers, Lee Chuen-Neng, MD, who heads **National University Hospital of Singapore**'s Department of Cardiac, Thoracic and Vascular Surgery. He also is chair of surgery at the **National University Health System**.

Tepnel launches DNA test for FH

Tepnel Life Sciences (Manchester, UK/Stamford, Connecticut) reported the launch of a DNA test for the early detection of familial hypercholesterolemia (FH), a genetic condition that predisposes individuals to high blood cholesterol levels and increased risk of cardiovascular disease.

The CE-marked Elucigene FH20 kit, validated for in vitro diagnostic use, can rapidly determine the 20 genetic mutations most commonly found in a UK-based population, that are responsible for the disease.

The company said the launch comes just prior to the expected release of clinical practice guidelines on familial hypercholesterolemia by the UK's National Institute for Clinical Excellence (NICE).

Tepnel said FH is a public health problem throughout the world, with an estimated 10 million people affected, the majority of who will suffer an adverse coronary event before they are 65 years old.

A common genetic disorder, the potentially lethal condition occurs in one of 500 people in Europe and North America. In the UK, it is estimated that up to 110,000 people are affected with FH and 75% of these cases are undiagnosed.

The NICE consultation on a draft of guidelines for use by the **National Health Service** in England and Wales is being finalized, with anticipated publication shortly. NICE is expected to recommend that all FH patients be offered a DNA test, with subsequent cascade screening to be performed where the mutation is identified in a patient. Following the confirmation of mutation status of an FH patient using the Elucigene FH20 assay, the Tepnel test can be used to detect other previously undiagnosed family members with FH through cascade screening programs.

In a recent UK pilot study, the test identified a 52% mutation detection rate in a sample of 110 FH heterozygous patients. "The study findings validate Elucigene FH20 as a valuable component for future FH screening programs in the United Kingdom, providing a cost-efficient and simple method for confirming a person has inherited this deadly condition," said Tepnel CEO Ben Matzilevich. "For effective treatment,

early identification of persons with FH is essential and FH20 offers the NHS the right tool at the right time to implement the new clinical practice guidelines."

The company said that pre-symptomatic identification of FH individuals "can ensure the health risks of high cholesterol are minimized through appropriate modifications to diet and lifestyle."

Six-month data show gains with CardioFit

BioControl Medical (Yehud, Israel) last month reported the publication of six-month data for eight of the more than 30 patients who participated in the European pilot study of its CardioFit device for congestive heart failure (CHF).

All eight patients were enrolled at the **Fondazione IRCCS Policlinico San Matteo** and the **University of Pavia** in Italy. The results were published in the September issue of the *European Journal of Heart Failure*.

The article was authored by the study's principal investigator, Peter Schwartz, MD, along with his research associates. The article, titled "Long-Term Vagal Stimulatyion in Patients with Advanced Heart Failure-First Experience in Man," describes the use of CardioFit's implantable vagal stimulation system in a pilot study designed to assess, for the first time ever, the feasibility and safety and possible efficacy of chronic vagal stimulation in CHF patients.

"A significant 40% improvement was observed in the commonly used Minnesota Living with Heart Failure Quality of Life questionnaire and in left ventricular end-systolic volume," Schwartz said. A favorable trend toward reduction was also observed in end-diastolic volume [and] despite their difficult baseline condition, the patients' NYHA functional class improved significantly."

The eight patients, all with advanced CHF, had a mean age of 54 years. Two to four weeks after implantation of CardioFit, vagal stimulation was initiated and intensity increased according to a prospective protocol. "It is our opinion as investigators that the CardioFit's novel approach to the treatment of patients with heart failure is feasible, and appears safe and tolerable," Schwartz said. "The preliminary efficacy results support the commencement of a controlled multi-center study in a larger population to confirm the seeming efficacy of the system."

"[Our] implantable neuromodulation technology has a wide range of applications," said Dr. Ehud Cohen, CEO of BioControl Medical. "To date, it is being applied to develop therapeutic devices in urology and for the treatment of congestive heart failure. In parallel with the development of these products, the company is also investigating applications for other indications."

He added, "The main focus of the company today is the initiation of an international, multi-center, pivotal study of the CardioFit system, which we believe will likely make a significant impact on existing clinical protocols once approved in the U.S. and Europe."

The company said details pertaining to the six-month data on the first 20 patients in the pilot study will be addressed in a presentation at the **American Heart Association**'s (Dallas) annual scientific sessions in New Orleans in November.

Hansen reports use of Sensei for AAA repair

Hansen Medical (Mountain View, California), a developer of flexible robotics and robotic technology for accurate 3-D control of catheter movement, reported that a team of physicians led by Professor Nick Cheshire at **St. Mary's Hospital** (London), part of the Imperial College Healthcare NHS Trust in London, used its Sensei robotic catheter system and Artisan control catheter to aid deployment of stent grafts used to treat an abdominal aortic aneurysm in a 78-year old patient.

The company said it believes this is the world's first procedure in which any robotic medical technology has been used to repair an aortic aneurysm through a patient's vascular system. "We have always believed vascular surgery would provide a very natural application for our Sensei and Artisan robotic technology, and the recent advancement at St. Mary's Hospital demonstrates what is already within reach for our technology in this field," said Fred Moll, MD, co-founder and CEO of Hansen. "Just as important, the recent experience of clinicians at St. Mary's Hospital clearly demonstrates what physicians can accomplish when they use Hansen Medical's advanced technology to provide more precise movement and control during different types of surgery."

"The time taken to correctly position a stent graft during the treatment of an aneurysm is highly variable and depends on the complexity of the vascular anatomy," explained Professor Nick Cheshire. "By providing increased catheter stability and accurate navigation, the Sensei system has the potential to greatly simplify the procedure and make it more predictable. In this case, it only took a few minutes to drive the Artisan catheter to the location where the stent was to be deployed."

An abdominal aortic aneurysm results from weakening and swelling of the artery's walls, often as people age, and is frequently fatal if it ruptures. When positioned across the weakened section, stent grafts act as scaffolding that can help prevent the aneurysm from bursting. This surgery was performed through accessing the patient's vascular system at the groin and using Hansen Medical's Sensei system to accurately navigate the Artisan catheter up into the weakened section of the aorta, where the stent grafts were placed.

French distributor for Hemotase MPH

CryoLife (Kennesaw, Georgia), a biomaterials, medical device and tissue processing company, reported that it has begun distribution in France, through **Laboratoire Gamida**, of Hemostase MPH for use in general, cardiac and vascular surgery.

CryoLife began distributing Hemostase MPH in the U.S., the UK and Germany in the 2Q08, and distribution in other markets is planned for later in 2008 and in 2009.

Hemostase MPH is developed using CryoLife's Microporous Polysaccharide Hemospheres technology (MPH), which yields a plant-based powder engineered to rapidly dehydrate blood, enhancing clotting on contact. This hemostatic agent facilitates the formation of a resilient, natural clot within just a few minutes.

Hemostase MPH received CE-mark approval in 2003 and FDA approval in September 2006.

Unlike many hemostatic agents, Hemostase MPH does not require additional operating room preparation or special storage conditions.

The company said pre-clinical evaluations have shown that Hemostase MPH does not promote infection and absorbs within 24 to 48 hours of application at the wound site, compared to other surgical hemostats that can take three to eight weeks or more to fully break down.

"As a complement to CryoLife's BioGlue product line, Hemostase MPH gives surgeons the ability to quickly control active surgical bleeding, and we are pleased to begin offering this product in France," said Steven Anderson, president/CEO.

Stereotaxis reports catheter use reintroduced

Stereotaxis (St. Louis) reported that the first atrial fibrillation (AF) procedures using its re-introduced partnered magnetic irrigated catheter were successfully performed in Europe last week.

The catheter received CE-mark approval in the last week of August following its resubmission to European regulators by the company's partner in July, and these first cases are part of the standard pre-release evaluation.

Also in July, the company's partner submitted a PMA supplement to the FDA for use of the magnetic catheter in the U.S. with the expectation that U.S. approval would be obtained subsequent to the CE mark.

Carlo Pappone MD, PhD, performed the first procedures last month at **San Raffaele University Hospital** (Milan, Italy).

Pappone said he was "delighted with the results of my first procedures performed successfully with the newly available Biosense magnetic irrigated catheter. I am extremely happy with its performance, and believe that Biosense did an excellent job. Contact stability, lesion quality and overall mechanical performance are excellent, and I believe safety is likely to be exemplary."

Bevil Hogg, CEO of Stereotaxis, said, "We are very pleased with the successful initial experience of our partnered magnetic catheter following its recent re-introduction in Europe. Most importantly, we anticipate that the commercial re-introduction of this catheter, which is used primarily for complex procedures in the left atrium of the heart, will mark a point of inflection in the utilization of our installed base of Niobe systems, resulting in a substantial increase in procedure volume over time and a concomitant acceleration of system sales."

Israel's Hadasit tests double lumen catheter

Hadasit (Ein Kerem, Israel) reported the successful pre-clinical testing of a prototype of the Double Lumen PCI Guiding Catheter for use in the treatment of coronary artery disease.

Unlike conventional catheters, the Double Lumen PCI Guiding Catheter has two lumens rather than one. The second lumen allows for a continuous medication infusion to the coronary artery during percutaneous coronary intervention (PCI), the part of the procedure when the narrowed coronary artery is dilated.

"The potential impact of this device is far-reaching," said Dr. Rafi Hofstein, Hadasit president/CEO. "The Double Lumen PCI Guiding Catheter has potential to change existing coronary artery PCI protocol for the better and to positively affect millions of patients worldwide."

He said the next step is to build a prototype for use in a proof-of-concept study in man and added that Hadasit is seeking partners to help finance the initiative.

Hadasit is the technology transfer company of Hadassah Medical Organization in Jerusalem, and promotes and commercializes HMO's continuously generated intellectual property and R&D capabilities.

CoveValve completes ReValving system cases

CoreValve (Irvine, California) reported that five clinical evaluation sites - two in New Zealand and three in Australia - have completed their first series of proctored cases using the company's proprietary ReValving system for percutaneous aortic valve replacement, featuring a porcine pericardium valve mounted in a self-expanding frame.

During a 12-day period, 24 patients at hospitals in Auckland, Brisbane, Melbourne, Sydney and Hamilton underwent successful percutaneous aortic valve replacement with the system. These hospitals are participating in a clinical evaluation registry as required for market clearance in Australia and New Zealand.

Acquisitions

• **MicroMed Cardiovascular** (Houston) is now a private company. The final step in the process was a reverse split of its common stock and a repurchase of fractional shares from the MicroMed shareholders holding smaller positions. At the time of the reverse split, **E-Wilson** (also Houston) had accumulated 97.5% of the outstanding MicroMed shares. The company said it received confirmation of the reverse split on Aug. 25, making E-Wilson the single shareholder of MicroMed. On Feb. 1, E-Wilson agreed to provide up to $10 million in financing in a series of advances over the next two years, subject to certain conditions. E-Wilson advanced $1 million to the company upon closing. In connection with the financing, the company issued an unsecured convertible note, under which E-Wilson had the option of converting the outstanding principal and interest due under the credit agreement into shares of the company's common stock at a conversion rate of $0.02 a share. The company agreed to seek stockholder approval of an amendment to its Certificate of Incorporation to increase the number of authorized shares of common stock from 100 million to 750 million shares. Unconverted amounts of principal accrue interest at a rate of 7.5% per annum and are required to be repaid over a 24-month period, beginning Feb. 28, 2011. On Feb. 20, E-Wilson converted a $1 million loan advanced Feb. 1 into MicroMed shares. The loan and accrued interest were exchanged for 50,205,500 MicroMed shares. Between Feb. 27 and April 28, E-Wilson bought the MicroMed shares held by several equity partners. Rodger Ford, shareholder and CEO of **SynCardia Systems** (Tucson, Arizona) and David Mackstaller, shareholder and VP-development of SynCardia, as a special purpose entity to own MicroMed shares, formed E-Wilson. MicroMed and SynCardia have some common shareholders, but are separate entities. MicroMed makes a small implant-able electric pump (the DeBakey VAD) that is intended to increase the cardiac output of a patient with a failing left ventricle. The DeBakey VAD and its related technology were developed in partnership with NASA.

• **Royal Philips Electronics** (Amsterdam, the Netherlands) has agreed to acquire **Alpha X-Ray Technologies** (Mumbai, India), a manufacturer of cardiovascular X-ray systems targeting the economy segment of the Indian market. Upon closing of this transaction in 4Q08, which is subject to certain contractual and other conditions such as regulatory approvals, Alpha will become part of the Cardiovascular X-ray business within **Philips Healthcare** (Andover, Massachusetts). Philips said that Alpha's product portfolio complements its existing high-end cardiovascular X-ray line.

Business Developments

Edwards tips scale to tissue over mechanical with Magna valve OK

By OMAR FORD
***CD&D* Staff Writer**
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It's not exactly the "paper or plastic?" debate, but chosing to go with a mechanical or tissue valve replacement is a question that patients with mitral valve failure must ponder. Until recently the popular choice has been to go with mechanical valves, since the devices provide strength and durability.

But there are drawbacks to taking the artificial route – the mechanical device makes a loud ticking noise and patients often must take anticoagulation medicines to prevent clotting. And the tissue valve replacement — which usually comes from pigs — route can be even less promising, because it is significantly weaker and can tear easily.

However, **Edwards LifeSciences** (Irvine, California) is hoping to add a new dimension to the debate with its newly FDA-approved Carpentier-Edwards Perimount Magna mitral heart valve.

The early September approval came three years after the tissue based-device was given the green light in the European market and is slated to be thrust into the U.S. market, where there are nearly 40,000 mitral valve replacements a year.

"Instead of using the pig tissue, we're using bovine pericardial tissue," Donald Bobo Jr., Edwards' vice president for heart valve therapy, told *Cardiovascular Devices & Drugs*. "The bovine tissue is stronger."

He said there are two main reasons why pig tissue valve replacements have become so contentious.

"The [problem] is that first, the tissue can calcify and close the valve," Bobo said. "Second, the leaflet tissue is pliable and is easier to tear. The bovine tissue is much stronger and can still calcify but it there aren't many occurrences of that happening. But we do have therapies to prevent calcification."

He added that the Carpentier-Edwards ThermaFix process is an anti-calcification technology that was developed to help mitigate tissue valve leaflet calcification, one of the primary causes of tissue valve deterioration.

The company said that the Perimount Magna valve is the first mitral tissue valve to feature an asymmetric shape that mimics the native mitral

anatomy. This design advancement, which it termed "significant and unique," provides what it said is the lowest effective profile and lowest ventricular projection for any tissue mitral valve in the industry.

In addition, the replacement valve is designed specifically to optimize patient blood flow and facilitates placement above the patient's native valve opening, which may allow surgeons to implant a valve that is larger than other conventional tissue valves.

"The Perimount Magna mitral valve represents a significant advancement for patients needing mitral valve replacement. It extends the exceptional hemodynamic performance and durability of the Magna valve platform to a design that is unique and specific to the mitral valve," Bobo said. "When surgeons see the new Perimount Magna mitral valve, they immediately appreciate that its design offers an advanced and easily implantable option."

The Perimount Magna mitral valve was launched in Europe in September 2005. It incorporates features of the Carpentier-Edwards Perimount mitral valve, which the company says has demonstrated 16 years of durability.

"This valve provides patients and surgeons with an important option for mitral valve replacement," said A. Marc Gillinov, MD, staff cardiac surgeon at the **Cleveland Clinic Heart and Vascular Institute**, and a paid consultant to Edwards Lifesciences. "The features of the valve, including its asymmetric shape, low profile and expansive sewing cuff, are designed to provide ease of implantation in a difficult valve position, low ventricular projection and strong hemodynamic performance."

Analysts say the Magna Mitral could better position the company to help address new surgical valve competition from **St. Jude Medical** (St. Paul, Minnesota) and **Sorin** (Milan, Italy). Edwards cited St. Jude and its Biocor implant as a key competitor in the market. Physicians have said Biocor is an easier device to implant than previous mitral valves from Edwards, thus taking market share from the company.

Biotronik EchoCRT study gets under way

Millions of people with heart failure could ultimately benefit from life-saving cardiac resynchronization therapy (CRT) if a new trial just underway proves that it helps.

Up to 70% of the 5 million Americans with congestive heart failure – those with narrow QRS – are currently treated with medication only and the prognosis for these patients is rarely good. In a new study, EchoCRT (Echocardiography-guided Cardiac Resynchronization Therapy), investigators are trying to determine if these patients could benefit from CRT.

The first implantation of **Biotronik**'s (Berlin/Lake Oswego, Oregon) Lumax CRT was performed in late August at **Ohio State University Medical Center** (Columbus), marking the beginning of the 1,250-patient trial.

EchoCRT is intended to demonstrate that optimal medical therapy plus CRT reduces all-cause mortality or first hospitalization for worsening heart failure in the study population compared to optimal medical therapy alone.

"Originally the trials to get CRT devices approved in the market in Europe and U.S. were based on patients with wide QRS with an electrocardiogram (ECG) anomaly that shows longer-than-normal ventricular activity. They represent only 30% of all subjects with chronic heart failure," Kevin Mitchell, Biotronik VP of clinical studies, told *CD&D*.

He added, "Years ago when CRT started, the studies were based on the idea that if you have mechanical synchrony you also have electrical. Now we know that there isn't a close correlation between electrical and mechanical defects."

Mitchell said it's the largest, prospective, randomized, double-blind, international, multicenter clinical trial of its kind, with 125 investigational centers worldwide, including sites in Australia, Canada, Israel, Europe and the U.S.

CRT is a treatment for heart failure patients experiencing conduction abnormalities and a lack of synchronization in the two ventricles. An implantable cardioverter-defibrillator (ICD) is surgically inserted to constantly monitor heart rate and rhythm. When it detects a rapid, life-threatening heart rhythm, the ICD delivers a large electrical impulse to the heart muscle to restore normal rhythm.

The EchoCRT study will randomize patients with heart failure, already receiving current standard pharmacological therapy, with a narrow QRS width (less than 130 ms) and echocardiographic evidence of left ventricular dyssynchrony.

"All of the patients enrolled will receive the device. Half will be programmed to CRT therapy on and the others will have it programmed off," Mitchell said.

The Lumax also includes Biotronik home monitoring. That data will be used in a pre-specified analysis to evaluate the frequency and duration of irregular heart rhythms. Patients will be followed for a mean duration of 24 months.

In recognition of its substantial clinical benefits, CRT is recommended in both the **European Society of Cardiology** guidelines and in the **American College of Cardiology/American Heart Association** guidelines for the diagnosis and treatment of chronic heart failure. But those guidelines have limited the application of CRT to patients with a QRS width of = 120 ms. EchoCRT will assess whether some of the remaining 70% of heart failure patients with "narrow QRS" could benefit from CRT therapy.

EchoCRT was designed under guidance from an executive steering committee of 11 academic specialists in electrophysiology, heart failure and echocardiography who considered earlier studies in developing the EchoCRT design.

"Chronic heart failure is associated with a poor prognosis with considerably shortened survival and repeated hospitalizations," said Frank Ruschitzka, MD, of the **University of Zürich**, executive committee co-chairman and international co-principal investigator of EchoCRT. "The vast majority of patients with heart failure present with a narrow QRS and do not currently receive CRT. The EchoCRT trial will test the hypothesis whether CRT improves outcomes in this large subset of heart failure patients."

DuraHeart recipient discharged after 15 days

The first U.S. patient implanted with a DuraHeart Left Ventricular Assist System (LVAS) from **Terumo Heart** (Ann Arbor, Michigan) was discharged in late August from the **University of Michigan Health System** (Ann Arbor), 15 days after receiving the device.

The company says the hockey puck-sized DuraHeart LVAS uses a new type of magnetic levitation technology (Mag-Lev) designed to eliminate mechanical contact within the blood flow path thus minimizing the chance of mechanical failure.

"We are extremely pleased with the performance of the DuraHeart and the recovery of our patient to an excellent functional state to permit discharge. We look forward to expanding upon our early experience with the DuraHeart in the near future," said Francis Pagani, MD, PhD, national co-principal investigator for the U.S. pivotal trial of the DuraHeart LVAS.

Terumo said the patient, a 62-year-old man from Livonia, Michigan, has been suffering from heart failure for nearly 20 years. The goal of these devices is to return the patient back to a relatively normal lifestyle and to provide improved quality of life, it said.

Mark White, marketing manager for Terumo Heart, told *CD&D* that the Mag-Lev technology is the core benefit of the DuraHeart, as it prevents a lot of the problems associated with other systems in which the impeller is suspended through pressure distribution.

With those systems, he said that when the pump is starting up for the first time, the impeller is just sitting on the bottom of the blood chamber, which can scratch the chamber surface and potentially create a source for cells to start clotting. He added that outside forces can potentially move the impeller, causing flow variations and even some areas of stagnant blood flow.

"Theoretically, if a patient is doing something really active like playing tennis, it's not inconceivable that it could deflect to the point of touching the chamber wall," White said. "You're relying on hydraulic characteristics to keep the impeller constant and centered and that's difficult to do."

The DuraHeart system, on the other hand, is controlled using position sensors to measure where it is and keep the impeller centered in the blood chamber. He compared it to playing with magnets and watching an object quickly snap to the middle of a magnetic field.

"It's rigidly positioned in the center of that chamber, regardless of what happens on the outside it never drifts out of that position," White said. "That gives you very consistent flow patterns . . . no stagnant-flow areas, there is never any contact with the chamber wall . . . that's really the core benefit."

He said there have not been any problems with blood clots in any of the DuraHeart systems that have been removed from patients, whereas other systems tend to have clotting issues. The company's engineers believe the Mag-Lev technology is responsible for keeping the devices clot free.

News of the first U.S. patient to receive a DuraHeart LVAS came almost simultaneously with **HeartWare** (Framingham, Massachusetts/Sydney, Australia) reporting that the first U.S. patient has received its LVAS at Washington Hospital Center (Washington), marking the start of its U.S. trial. Similar to the DuraHeart, the impeller that spins inside the HeartWare LVAS pump is also suspended by magnetic forces. Although both pumps are much smaller than earlier generation devices, the HeartWare is actually small enough to fit directly adjacent to the heart in the pericardial space. Most other systems, including the DuraHeart, are implanted into a surgically-created pump pocket in the abdomen.

Other companies developing similar devices include **Ventracor** (Chatswood, Australia), **Abiomed** (Danvers, Massachusetts) and **Thoratec** (Pleasanton, California).

Earlier this year Terumo received the go-ahead from FDA to start its U.S. trial of DuraHeart as a bridge-to-transplant device (MDD, March 5, 2008). The company also reported a couple months ago that the Institutional Review Board of the University of Michigan Health System voted to move forward with the trial (MDD, June 30, 2008). The trial is expected to enroll 140 patients at up to 40 centers.

In addition to the hockey puck-sized pump, the DuraHeart consists of the following components: an inflow conduit (a small titanium tube connecting the pump to the heart); an outflow conduit comprised of Vaskuteck Gelweave that is sewn to the aorta; a small battery-powered controller that serves as the brain of system and is worn or carried by the patient; and the hospital console, which allows doctors and hospital staff to monitor and have a degree of control over the pump.

Earlier-generation left ventricular assist devices

(LVADs) are prone to hemolysis, blood clots and mechanical failure, Terumo noted. The company said it has tried to overcome these problems by combining the Mag-Lev technology and a centrifugal pump. The device has been used in more than 70 patients in Europe with the longest ongoing support more than three years. The device is intended to provide cardiac support for patients awaiting transplant who are at risk of death due to end-stage left ventricular failure.

Eventually, the company would like to get a "permanent" indication for the DuraHeart, in addition to the bridge-to-transplant indication. White said a trial for that indication is planned, but has not started yet. He said the permanent LVAS use market is much bigger than the bridge-to-transplant market because there are only about 2,000 donor hearts available and the criteria to receive a new heart is rather strict.

Cordis wins partial victory in Voda appeal

Patent lawsuits continue to dot the landscape for makers of medical devices, and **Cordis** (Miami Lakes, Florida) is only one of a number of device firms embroiled in a number of such suits, the pace of which seems to be increasing. Cordis last month managed to win a partial reversal of a juried court case that awarded Jan Voda, MD, of Oklahoma City, Oklahoma, potentially multiple millions of dollar in damages for what he alleges is an infringement of his design for a catheter. However, a new precedent that was set after the conclusion of that initial trial gave the defendant enough room to blunt some of the effect of the suit.

Voda sued the company in 2003 over the company's XB catheter and won handily with the damages set at 7.5% of gross sales despite the fact that Cordis went to market with the first iteration of the XB before Voda filed a patent for his invention. The crucial change to the original XB was a change in the catheter to a slightly curved design that apparently failed to be curved enough to avoid infringement of a catheter described as "straight," among other things.

The suit alleged that Cordis willfully infringed on the physician's patent and prior to the end of the first trial, Voda expanded the jurisdiction of his suit to four other nations, Britain, Canada, France and Germany.

The Federal Circuit Court of Appeals for the Western District of Oklahoma ruled on Aug. 18 that the lower court's instructions to the jury regarding willfulness were erroneous. The notion of willfulness in this context was affected by a lawsuit involving computer hard drive maker **Seagate Technologies** (Scotts Valley, California). That suit, which was decided in August 2007, is said to have lowered the bar for defending allegations that a defendant willfully infringed on a patent. The first trial in *Cordis v. Voda* concluded before the Seagate trial had run its course, but the appeal came after the closure of the Seagate trial, hence the application of that standard for willfulness.

The Circuit Court overturned the jurisdiction claim based on the lack of a provision affirming such a claim in the Paris Convention for the Protection of Industrial Property of 1883. However, the Paris Treaty does not ban such a claim, either. Voda also lost a motion to slap an injunction on Cordis' distribution of the XB.

Software snag leads to AED recall

Physio-Control (Redmond, Washington), maker of external defibrillators, has been in the news quite a bit over the past year and a half, and is now drawing more ink because of a recent class I recall of 249 units of its LifePak CR Plus automated external defibrillators (AEDs). The company initiated the recall because the units were loaded with software written for its semi-automated AEDs.

According to the Sept. 11 statement, the company already had completed the recall of the affected units, which when activated would display a prompt to "press the shock button to deliver therapy," according to the statement. Physio-Control indicated that the shock button is covered on the automated units and as a consequence, "it is possible that therapy could be delayed or not delivered at all, possibly resulting in death."

The company notes that one complaint has surfaced in connection with one of the affected units and that as of Sept. 2, it "has notified all affected customers and shipped replacement devices at no charge." In the meantime, the company recommends that customers either remove the unit or "remove and discard the shock button cover" per instructions it has provided.

The firm's owner, **Medtronic** (Minneapolis), had attempted to spin off Physio-Control last year, but production problems halted the plan. Medtronic signed a consent decree with FDA earlier this year over quality problems at Physio-Control's plant in Redmond, but FDA's warning letter database indicates no issuance of a warning letter.

Ann Devine, public relations manager at Physio-Control, told *CD&D* that the problem with the incorrectly downloaded software was due to a "keying-in error." She also said that the hardware design of the LifePak CR fully automated unit is essentially the same as the semi-automated unit for which the software in question was written, hence the availability of the shock button on the automated version.

Regarding the company's persistent problems with regulations governing good manufacturing practices, Devine said, "We're working very closely with FDA and with a third-party auditor" to bring operations into compliance. She said the company and FDA have not yet set up a future inspection date to check on the company's corrections.

New guidance for ultrasound 510(k)s

FDA has published a new guidance for those "seeking marketing clearance of diagnostic ultrasound systems and transducers."

The 68-page guidance covers intravascular ultrasound catheters and cardiovascular blood flow meters as well as ultrasonic pulsed Doppler imaging systems. One thing has not changed, the guidance notes, informing the reader that the guidance "retains the two-track approach of the 1997 guidance." Track 1 recommendations "are for devices that do not conform to the output display standard," whereas those for track 3 deal with devices that do conform to that standard.

Agreements

• **Aetna** (Hartford, Connecticut) reported that it has reached agreement with the **Central Florida Health Alliance** (Orlando) on a three-year contract that adds **Leesburg Regional Medical Center** (Leesburg, Florida) and **The Villages Regional Hospital** (Villages, Florida) to Aetna's provider network in the Central Florida area. The agreement takes effect Sept. 15. Under the agreement, members of Aetna network-based plans will be able to receive covered inpatient and outpatient services, at in-network rates, from Leesburg Regional Medical Center and The Villages Regional Hospital. Aetna provides and administers health benefits to more than 225,000 members in Central Florida. Those members have access to a contracted network of 35 hospitals, 1,626 primary care physicians and 4,434 specialists. The Villages Regional Hospital, part of Central Florida Health Alliance, is a 198-bed, acute-care hospital located in the heart of The Villages, a nationally-known adult community. The facility serves the tri county area – Lake, Sumter and south Marion counties. Leesburg Regional Medical Center, also part of Central Florida Health Alliance, is a 309-bed, acute-care hospital with specialty services including comprehensive cardiovascular, neurosurgery, and the only designated stroke center with the Joint Commission Seal of Approval in Lake and Sumter counties.

• **Hatch Medical** (Duluth, Georgia), a medical device incubator and technology brokerage firm, said it has agreed to broker **Evexar Medical**'s (Bromley, UK) self-expanding, collagen-based sealing technology, EndoSeal. According to Evexar, Endovascular aortic repair was introduced in the mid 1990's as a minimally invasive alternative to open surgical repair and was aimed at reducing many of the associated risks with current surgical techniques. Unfortunately, while aortic endografts provide numerous benefits, complications often follow this procedure, the company said. One of the more significant complications is an endoleak, a condition often attributed to a poor seal between the endograft and the native vessel at its extremities. Such endoleaks, if left untreated, predictably result in ongoing pressure in the aneurysmal sac with the associated risk of rupture. Evexar says its technology effectively seals gaps that can occur between an endograft and an irregular vessel wall, ensuring a secure seal and substantially reducing the possibility of endoleaks. "We are very pleased to be working with Evexar Medical and believe that the EndoSeal technology will provide innumerable benefits and greater procedural options for clinicians, patients and endograft manufacturers by reducing the long-term complications associated with endograft placement," said Paul Gianneschi, managing principal and founder of Hatch Medical.

• **Novation** (Irving, Texas), a healthcare contracting services company of **VHA** (Irving, Texas), **University HealthSystem Consortium** (Oak Brook, Illinois) and **Provista** (Irving, Texas), said it has added **Guidant** cardiac rhythm management devices to its **Boston Scientific** (Natick Massachusetts) agreement. The Cognis CRT-D and the Teligen ICD are among the world's smallest and thinnest high-energy devices at 32.5 cc and 31.5 cc respectively, while less than 10 mm thick. Both devices offer features based on substantial engineering advances, including extended battery longevity over previous company devices, self-correcting software and improved programming technology. The contract addition was effective Aug. 1.

• **OmniSonics Medical Technologies** (Wilmington, Massachusetts), a developer of devices for use in the treatment of vascular disease, reported that it has entered into a licensing and development agreement with **Boston Scientific** (Natick, Massachusetts) for technology to treat thromboembolic acute ischemic stroke. Treatment of this type of stroke represents a significant unmet clinical need, as only 10% of the more than 600,000 stroke patients in the U.S. receive therapy each year, the companies said. The two companies will work jointly to develop an application of OmniSonics' OmniWave technology for the treatment of acute ischemic stroke. The OmniWave technology, which delivers low-power ultrasonic energy to remove thrombus (or a blood clot), recently was launched in the U.S. for the treatment of clots in the peripheral vasculature. Boston Sci will provide funding based on the achievement of development milestones and has an option to acquire the technology as well as exclusive rights to the intellectual property for the treatment of acute stroke.

Market Updates

Shocks linked to a higher rate of death challenge ICD therapy

By AMANDA PEDERSEN
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The primary purpose of an implantable cardioverter-defibrillator (ICD) is to stave off a heart attack.

But a study published in the Sept. 4 issue of the *New England Journal of Medicine* (*NEJM*) will have patients wondering about the benefits of these devices because the study concludes that heart failure patients with an ICD who receive therapeutic shocks from the device have a "substantially higher" risk of death than those who do not receive shocks.

Responding to the study, various industry organizations were quick to emphasize the continuing therapeutic importance of ICDs.

Using data from the Sudden Cardiac Death in Heart Failure Trial, Jeanne Poole, MD, and her colleagues followed the cases of 811 people with defibrillators and found that any shock increased the risk of death.

The study found that those receiving an appropriate life-saving shock were six times more likely to die, compared to those not receiving a shock. Additionally, the study found that 30% of these deaths come within a day of the jolt, the researchers found.

Additionally, an inappropriate ICD shock, as compared with no inappropriate shock, was associated with a significant increase in the risk of death. And for patients who survived longer than 24 hours after an appropriate ICD shock, the risk of death remained elevated

The study authors said the most common cause of death among patients who received any ICD shock was progressive heart failure.

Poole, of the **University of Washington** (Seattle), said, "The most important thing to remember is that the defibrillators save lives," and that a defibrillator shock may be a danger signal that patients and doctors should heed.

The **Heart Rhythm Society** (HRS; Washington) issued a statement with its interpretation of the findings: that the patients who received shocks were in worse health than those who did not need to be shocked. Thus, HRS interpreted the increased death rate as related to the patient's overall health rather than the device itself. HRS said that ICDs are 99% effective in stopping life-threatening arrhythmias, calling the devices the most successful therapy to treat ventricular fibrillation, the major cause of sudden cardiac arrest.

The **Advanced Medical Technology Association** (AdvaMed; Washington) issued a statement saying it is important to put the study results in the context of the significant overall patient benefit of ICDs. "First and foremost, ICDs are incredibly successful in achieving their primary purpose: saving lives," said David Nexon, senior executive VP of AdvaMed, in the statement.

In an editorial accompanying the study, Jeff Healey, MD, and Stuart Connolly, MD, say it is "somewhat disturbing to realize that actually receiving a shock is such an important predictor of death." However, they note that it should not be surprising that many patients in whom sudden death from arrhythmia is averted by an ICD ultimately die from heart failure.

"In severe chronic conditions, most worthwhile interventions only modestly delay death. If a specific therapy is effective against only one cause of death and does not address the underlying disease process, then death from competing causes is inevitable," Healey and Connolly write. They also note that it is plausible, though unlikely, that ICD shocks somehow have an adverse effect on myocardial function.

Study: CAS as effective as CAE 'medium term'

Two studies appearing in the Sept. 6 issue of *The Lancet Neurology* concludes that to prevent ipsilateral stroke in patients with stenosis of the cartoid artery, carotic angioplasty with stenting (CAS) shows a similar level of effectiveness as the surgical procedure for clearing the carotid, termed carotid artery enarterectomy (CAE). Both trials conclude that CAS is an appropriate alternative to CAE in the medium term. However, they also found a greater risk for stroke following CAE 30 days after the procedure and that this must be taken into consideration. This risk can be reduced, the studies conclude, through a better set of criteria to select patients.

Thus far, CAE has been considered the standard procedure. The less-invasive CAS procedure widens and reinforces the vessel using a stent, but the procedure may not remove the plaque or it may loosen debris, providing a risk of stroke and other complications.

Researchers in the Stent-Protected Angioplasty Versus Carotid Endarterectomy (SPACE) randomized trial examined CAE and CAS in 1,214 patients in Germany, Austria, and Switzerland. The rates of ipsilateral ischemic stroke and restenosis were measured up to two years after the procedure, with blockage recur-

rence of at least 70% of the vessel diameter evaluated by ultrasound.

In patients with stents, blockage recurrence was more common (10.7%) in comparison with patients who had the CAE procedure (4.6%). But, there was no significantly increased risk in this group for ipsilateral ischemic stroke in comparison with the surgery patients (9.5% vs. 8.8%).

A long-term follow-up looked at 527 patients at 30 different centers in France to find the composite outcome of any stroke, or death within 30 days of undergoing CAS (265 patients) or CAE (262 patients). Though stented patients had twice the risk of this outcome, stroke was usually soon after the procedure (within 30 days) and there was no difference in risk of ipsilateral stroke after a stroke occurred in this group. After this initial period, in the medium term, therefore, CAS seems as effective as CAE.

In an accompanying commentary, A. Ross Naylor of the **Leicester Royal Infirmary** recommended future directions for research in the field of CAS. He wrote: "The mid-term to long-term results . . . add substantially to the body of data from randomized trials that compare CEA with CAS for the management of patients with severe carotid disease who have recently developed symptoms."

He said that the most important findings from the studies "is recognition that the average annual risk of ipsilateral stroke is 1% or less, irrespective of whether the patient was treated by CEA or CAS."

Study downplays side effects of ICD therapy

Contrary to the above report, another study in the same issue of the *NEJM* offered a significantly positive view of this therapy, concluding that ICDs not only reduce the risk of death but also offer no significant alteration in the patient's quality of life.

Researchers at **Duke University Medical Center** (Durham, North Carolina), say their study is the longest and most comprehensive analysis of ICD use and that the findings should ease physician and patient concerns about the side effects of this therapy. "Basically, we wanted to find out if ICD therapy improves longevity but only at the cost of worse quality of life," says Dr. Daniel Mark, a cardiologist at Duke and the lead author of the study.

Mark and colleagues studied 2,521 patients enrolled from 1997 to 2001 in the Sudden Cardiac Death in Heart Failure Trial, with all participants receiving what was billed as "state-of-the-art" medical therapy for heart failure. One-third of the patients were randomly assigned to receive an ICD, a second group was assigned to receive the antiarrhythmia drug amiodarone, and a third group took an amiodarone placebo. Researchers interviewed each participant four times over a 30-month period to assess disease status, physical and social activity levels, psychological well-being and ability to perform routine daily tasks.

While members of all groups had essentially the same scores on psychological well-being at the beginning of the study, patients with the ICDs had somewhat higher quality of life scores at three and 12 months, when compared to those in the other groups. Scores of other quality-of-life measures also improved over a short term among ICD users, but all differences diminished over time and disappeared at 30 months.

Multiple molecular markers point to MI

A study led by investigators from **Massachusetts General Hospital** (MGH; Boston) and the **Broad Institute of Harvard and MIT** (Cambridge) concludes that a new technique that measures hundreds of molecular markers in the blood can identify those released when cardiac tissue is injured by a lack of oxygen. The report appears in the October *Journal of Clinical Investigation*.

Senior author Robert Gerszten, MD, of the MGH division of cardiology and Center for Immunology and Inflammatory Diseases, said, "Right now there are no blood markers for reversible myocardial injury in clinical use, and the only available markers are not detectable until hours after the onset of tissue damage. Because our treatments for heart attacks are most effective in the first hours after symptoms occur, these newly identified markers could help us apply treatments sooner and help more patients."

The research team took advantage of a procedure that is, in essence, a planned heart attack. In a condition called hypertrophic cardiomyopathy, bloodflow out of the heart is obstructed by a massive thickening of the wall between the left and right sides. This tissue overgrowth can be treated with the technique of septal ablation that destroys the excess tissue, a scenario that mimics the damage that happens to heart muscle when its blood supply is cut off.

The researchers analyzed blood samples from 36 patients taken before and at several time points after septal ablation. Using advanced mass spectrometry that can assess hundreds of metabolites in as little as 10 minutes, they identified several that significantly changed right after the ablation process, a time period during which currently available markers remained unchanged. The changes seen in the first 10 minutes persisted an hour later, and analysis of blood from veins in the coronary circulation confirmed that the heart was the source of the changes.

Comparing the results of these "planned" heart attacks with blood samples from patients with spontaneous coronary blockages found four metabolites that increased in response to ablation and also were elevated in patients with true heart attacks, confirming them as markers of myocardial damage.

Product Pipeline

After PAS-Port OK by FDA, Cardica's shares jump by 35%

By OMAR FORD
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Doing business in med-tech is at once both complicated and simple. As an example of the latter, a nod from the FDA is all a company needs to make some serious headway in the market.

Take **Cardica** (Redwood City, California) for example. Shares for the California-based company shot up more than 35% at $10.70 a share on the same mid-September day that it issued a press release noting 510(k) clearance to market its PAS-Port Proximal Anastomosis System for use in cardiac bypass surgery in the U.S.

Until now, the system was limited to sales in Europe and Japan, but FDA approval opens up a floodgate of patients who're looking for a safer, less-intrusive means of cardiac bypass surgery.

"With the introduction of the PAS-Port system in the U.S., cardiothoracic surgeons are now provided with a complete package of reliable, automated revascularization systems for use in CABG procedures," President/CEO Bernard Hausen, MD, PhD, said during a conference call.

He added, "We believe that by replacing hand-sewn sutures, our automated proximal and distal anastomoses systems can help cardiovascular surgeons perform consistent, reliable anastomoses with even the smallest of vessels, giving surgeons greater ability to use minimally invasive techniques for cardiac surgery."

Hausen said Cardica plans to launch PAS-Port in the U.S. in the next several weeks with "a systematic and deliberate roll-out to surgeons and [we] look forward to training 50 to 60 surgeons per quarter, as we previously have discussed."

The device creates a secure connection between the body's main artery and vein grafts. It differs from the current method of connecting a bypass graft vessel to the aorta in CABG surgery, which often requires that the aorta be clamped and utilizes time-consuming, hand-sewn sutures. When the clamp is released, tiny blood clots or particles from the aortic wall can be released, which can travel to the brain and cause stroke and other neurologic complications.

The company said the PAS-Port system allows a surgeon to complete an automated proximal anastomosis without the need to clamp and manipulate the aorta. Eliminating the clamp may greatly reduce the risk of particle release and ensuing neurocognitive events, it said.

Put another way, this means an attachment to a vessel of 3 mm or more in diameter, using a clamping or "coupling" approach, compared to connection to a vessel of just 1 mm in diameter, using the delicate stapling method.

"PAS-Port leaves no metal or aluminum in the graft and it reduces occurrences of restenosis," Hausen said, calling the device a "major milestone". The system's design allows surgeons to load the bypass graft into the system and rapidly complete the anastomosis, typically in about a minute.

This reduces the time required for the anastomosis while providing a consistent, reliable connection. The bypass graft is loaded into the system without damaging endothelial cells, while maximizing the orifice, which is especially important with a small graft. No metal is within the lumen of the graft vessel.

According to results from the pivotal clinical trial of the PAS-Port system, anastomosis surgical time is significantly reduced compared with hand-sewn anastomoses. Patient outcomes may be improved due to shortening of surgery times and hospital stays and reducing complications associated with aortic clamping.

Cardica conducted a 220-patient, prospective, pivotal, randomized trial of PAS-Port at 12 sites in the U.S. and Europe. The trial compared venous bypass graft vessel connections to the aorta made using the PAS-Port system versus those made using conventional hand-sewn sutures. Results showed that the study met its primary endpoint of non-inferiority to hand-sewn anastomoses, as well as all other primary and secondary endpoints.

As of June 30, more than 8,800 PAS-Port systems had been sold worldwide, with the vast majority of units deployed in Japan. According to Cardica's Japanese distributor, the PAS-Port system is used in more than 20% of all proximal anastomoses performed using a vein bypass graft during CABG surgeries in Japan.

Cardica expects to have 50 to 60 surgeons trained to use the device per quarter.

Elsewhere in the product pipeline:

- The National Institutes of Health (NIH) has informed **CHF Solutions** (Brooklyn Park, Minnesota) that the CARRESS-HF trial has begun enrolling patients. Sponsored by NIH's National Heart, Lung, and Blood Institute and chosen out of 16 national submissions for studies in heart failure, this study will compare CHF Solutions' Aquapheresis therapy with

standard medical drug therapy in patients hospitalized with acute decompensated heart failure and cardiorenal syndrome. Fluid overload can be caused by problems with the heart, kidneys, liver and lungs, and is frequently experienced after surgical operations, trauma, and burns. The leading cause of fluid overload is congestive heart failure (CHF), sometimes referred as just heart failure. Heart failure is a condition that affects about 5 million Americans and is responsible for over 3.1 million primary and secondary hospitalizations annually. CHF Solutions' Aquapheresis therapy is a mechanical method to safely and effectively remove the excess salt and water in patients with fluid overload.

• **Digirad** (Poway, California) reported the initial clinical trial of a new imaging system, Cardius X-ACT, using new technology to correct attenuation, or image distortion, an inherent issue in cardiac SPECT imaging. Cardiac SPECT (single photon emission computed tomography) — also called myocardial perfusion imaging — is a non-invasive test to assess the heart's structure and function. Small amounts of radioactive substances are injected into a patient's vein, and special cameras produce images of the heart. These SPECT images are used to identify blockages in coronary arteries, determine whether a patient has had a heart attack, evaluate risk of a heart attack, and assess condition after bypass surgery or angioplasty.

• **Edwards Lifesciences** (Irvine, California) has presented new data on the Edwards Sapien transcatheter heart valve with the Ascendra transapical delivery system. The SOURCE trial is designed to evaluate commercial use of the Sapien valve with a prescribed training and proctoring program. It is a registry of procedural and short-term clinical outcomes. The current data reflect 309 cases at hospitals in 12 European countries. Survival at 30 days was 88%.

• **iCardiac Technologies** (Rochester, New York) reported the completion of what it said is the industry's largest validation study for an automated ECG analysis technology. The company said the results of the study make iCardiac's technology the first to comply with the FDA E14 industry guidance. In the validation study, iCardiac's automated QT method has demonstrated results equivalent to manual measurements performed independently by U.S. board-certified cardiologists. The automated QT method was shown to reliably detect the effect of the drug moxifloxacin. Moxifloxacin is used as a positive control in cardiac safety studies and is included in the FDA's E14 industry guidance. QT analysis is part of iCardiac's software platform, COMPAS 3.0. The platform provides comprehensive analysis of cardiac repolarization signals and contains several advanced arrhythmia biomarkers, as well as ECG signal processing tools.

• **Inverness Medical Physician Diagnostics Group** (San Jose, California), a division of **Inverness Medical Innovations** (Waltham, Massachusetts) reported the launch of the INRatio2 PT/INR monitoring system, a portable device that measures blood-clotting time, also known as prothrombin time, using one drop of blood from a patient's finger. The INRatio2 is used by healthcare professionals and their patients in the management of warfarin, a blood-thinning drug, to monitor the effectiveness of the drug and warn of potential blood clots and other bleeding risks. The INRatio2 PT/INR has been cleared by the FDA for warfarin patients to test themselves at home, offering patients quick access to their PT/INR results. The test results are then transmitted to their treating physician by telephone or internet.

• **Medtronic**'s (Minneapolis) Talent thoracic stent graft is safe and effective compared to open surgery, according to research published by the **Society for Vascular Surgery** (SVS; Chicago) in the September issue of the *Journal of Vascular Surgery*. The FDA approved the device in June for certain aneurysms of the descending thoracic aorta, but has been available outside the U.S. since the late 1990s. "The Talent thoracic device, first of all, carries a legacy of experience. It is the most implanted thoracic device in the world, it has been available outside the U.S. since 1997," Simona Zannetti, MD, senior director of clinical affairs for Medtronic Endovascular Innovations, told *CD&D*. The Talent system is designed to provide a minimally-invasive treatment alternative to open surgery for patients with life-threatening aneurysms in the upper portion of the aorta, the body's largest artery. Thoracic aneurysms affect about 30,000 people a year in the U.S., causing thousands of deaths. The procedure involves threading the stent graft through a small opening in the femoral artery of the leg. The graft is advanced under fluoroscopic guidance to the site of the thoracic aortic aneurysm, where it is then positioned and deployed from the delivery system. Once deployed, the stent graft expands to fit snugly within the diameter of the aorta, providing a new path for the blood flow.

• The **Sorin Group** (Arvada, Colorado) reported the first successful uses in the U.S. of its newest pediatric devices for cardiovascular surgery. The Dideco KIDS D101 pediatric oxygenator and the Dideco KIDS D131 pediatric arterial filter have now been successfully used by Children's Medical Center Dallas during dozens of cardiac surgery procedures for pediatrics. The Dideco KIDS D101 oxygenator is designed to minimize hemodilution and reduce foreign surface area exposure; the D101 is specially proportioned to the pediatric patient. Its low surface area results in a more balanced oxygen and carbon dioxide transfer, and the innovative D101 design has the low priming

volume of 87 mls while addressing the cardiopulmonary bypass needs of pediatric patients. The Sorin Group makes cardiac surgery devices.

• **St. Jude Medical** (St. Paul, Minnesota) has developed an implantable cardiac monitor (ICM) the size of a computer thumb drive designed to provide more accurate sensing of abnormal heart rhythm signals in difficult-to-diagnose cases in which standard monitoring tests are not enough. FDA has cleared the SJM Confirm ICM, which it says will help physicians diagnose and document difficult-to-detect rhythm disorders in patients who may suffer from unexplained symptoms, including fainting, palpitations and shortness of breath. At 6.5 cc, the Confirm is the smallest ICM on the market, according to the company. The device is implanted just under the skin in the upper chest region during an outpatient procedure under local anesthesia. "It is the smallest cardiac monitor available, it provides real time data and some devices that are out there do not do that," Kathleen Janasz, a St. Jude spokeswoman, told *CD&D*. Janasz also said it was important that the Confirm ICM is approved for syncope (or, fainting), which is "one of the most difficult diagnoses to make." According to St. Jude, syncope is responsible for about 3% of all emergency room visits and up to 6% of all hospitalizations.

• Patients with heart failure who no longer get symptom relief from medications may have a new treatment option on the horizon with FDA's conditional approval last month of an investigational device exemption (IDE) to **Sunshine Heart** (Sydney, Australia) to begin its first U.S. clinical trial for the C-Pulse, an implantable aortic cuff heart assist device. "Almost 1.4 million patients have moderate heart failure," Sunshine CEO Donald Rohrbaugh told *CD&D*. "Thirty percent have an electrical disorder and pacemakers are addressing this problem. But that leaves 70% with a large unmet clinical need. They have a progressive condition and they often end up with end-stage heart failure." Sunshine's cuff, which functions like a blood pressure cuff, wraps around the aorta and a balloon inflates to displace blood in the aorta. It's being positioned as a Class III heart failure therapy that offers an intervention bridging the clinical gap between heart failure pacemakers and end-stage therapies. Implantation is performed via a simple surgery on a beating heart, without the need for heart-lung bypass or any incisions to the heart or great vessels. Enrollment is expected to begin at six U.S. medical institutions by the end of 2008.

• **Volcano** (San Diego) reported the use of its VH IVUS in GlaxoSmithKline's IBIS-2 trial. In the study, Volcano's VH IVUS technology demonstrated and quantified compositional changes in atherosclerotic plaque that occurred over time. In IBIS-2, VH IVUS showed compositional changes in the placebo group that suggest continued progression of necrotic core despite standard of care therapy. Use of the novel Lp-PLA2 inhibitor, darapladib, plus standard-of-care therapy prevented this progression. VH IVUS is a catheter-based technology that creates colorized tissue maps of plaque composition in real time. The technology uses spectral analysis techniques to allow simplified interpretation of ultrasound images and provide detailed information on the composition of each patient's atherosclerotic plaques. The color VH images show four plaque component types: necrotic core, dense calcium, fibrous and fibro-fatty.

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