

CARDIOVASCULAR DEVICE UPDATE

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Focusing selective therapy on cardiovascular disease

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CHICAGO — Cardiovascular disease — the leading cause of death in the U.S. and a major cause of morbidity — also comprises one of the top components of healthcare cost, not only in America but also in most developed countries. As these costs have continued to spiral upward, pressures to limit the cost burden due to cardiovascular disease have increased, driving efforts by physicians and healthcare administrators to develop new approaches to controlling the cost of healthcare.

**CDU at the
American
Heart
Association**

These conflicting pressures were discussed here by Raymond Gibbons, MD, president of the **American Heart Association** (AHA; Dallas), at the opening session of the association's Scientific Sessions. Gibbons noted that healthcare spending now accounts for 21% of the federal budget, and healthcare expenses for U.S. corporations are likely to exceed net profits by 2008.

While limiting access to healthcare is one possible solution to address rising costs, there is a general feeling that wholesale rationing of healthcare is not likely to be accepted by most Americans. However, an alternative now beginning to materialize within the healthcare system — including the segment involved with cardiovascular disease — is more selective use of costly diagnostic and therapeutic modalities.

Ultimately, personalized medicine may provide the most effective approach for tailoring the utilization of healthcare technologies to optimize cost as well as outcome. For now, though, there is an increasing emphasis on more selective use of medical technology, particularly for new, high-cost technologies such as drug-eluting stents (DES), implantable cardioverter defibrillators (ICDs) and advanced diagnostic imaging technologies.

DES sees decline

Certainly, other factors have recently played a role in limiting the utilization of DES and ICDs, such as safety and reliability issues that have arisen concerning these technologies. The issue of late stent thrombosis has resulted in a decline in

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the proportion of patients receiving DES devices in the U.S., from a level of more than 90% of percutaneous coronary intervention (PCI) procedures in many centers to levels of 80%-85%. Even more selective use of DES has been advocated by some cardiologists, with a target of 50%-55% proposed by some and currently the prevailing rate in Europe.

Not unexpectedly, the lower utilization level in Europe has been driven less by concerns about device safety and more by issues of costs — both the costs of the devices themselves and also the associated dual anti-platelet therapy required that typically runs about \$4 per day and must be continued for three to six months.

In addition, the true extent of the added risk of adverse events for DES compared to bare-metal stents (BMS) has not been definitively quantified, and it ultimately may not prove to justify any reduction in use, particularly as second-generation DES devices become available. But cost issues will remain, and will continue to be a driver for more selective DES use.

Among the approaches being developed to enable better selection of patients for interventional therapy are advanced technologies for plaque characterization, which promise not only to allow matching of device characteristics to lesion type, but also to dictate use of alternative, less costly disease management approaches in some patients.

A focus on interventional

Other advances in interventional therapy highlighted at the AHA sessions included carotid stents, devices for closure of heart defects such as patent foramen ovale (PFO), percutaneous valve implantation and catheter-based treatments for arrhythmia.

A new study presented at the conference also revealed issues with the timely delivery of interventional therapy, finding that 80% of treatment centers in the U.S. fail to initiate therapy within the 90-minute time window specified by the latest guidelines from the AHA and the **American College of Cardiology** (Washington). Resolving those deficiencies could drive growth in demand for rapid diagnostic technologies to speed patient triage in the emergency room, as well as for improvements in hospital infrastructure to optimize efficiency. A number of simple strategies were identified in the study that can also help reduce treatment delays, such as early activation of the cath lab and more rapid response by cath lab staff when paged.

The type of therapy that is most appropriate for patients with coronary disease continues to be a topic of continuing and significant debate. For coronary artery occlusions or stenoses — the cause of myocardial infarction and angina — interventional treatment using angioplasty and stenting is increasingly the preferred approach. As discussed by Cindy Grines, MD,

of **William Beaumont Hospital** (Royal Oak, Michigan) at a symposium held in advance of the AHA sessions, about two times as many patients who present with ST-segment elevation myocardial infarction (STEMI) are now treated with primary angioplasty/stenting as are treated with thrombolysis, which was at one time the preferred modality.

Recent studies have demonstrated improved outcomes for primary PCI, regardless of the delay in starting therapy. In fact, studies have shown that there is no advantage to giving thrombolytic therapy before the patient arrives at the hospital if primary PCI is performed, and also no advantage in adding thrombolysis to PCI (so-called facilitated PCI). Rather, mortality rates after treatment are somewhat higher for patients treated with facilitated PCI.

Instead, Grines recommended giving anti-coagulants such as clopidogrel when a STEMI patient arrives at the emergency department, and then proceeding to PCI as quickly as possible. Other approaches to improving outcome for myocardial infarction patients, such as removal of thrombus via clot maceration and aspiration, or the use of filters or occlusion balloons during PCI to avoid embolization due to debris created during the procedure, have produced disappointing results.

In the case of DES vs. BMS

The use of DES versus bare-metal stents (BMS) is another area of controversy that was discussed in numerous sessions at the AHA conference. The issue of late-stent thrombosis with DES has become one of the most widely debated topics in interventional cardiology in 2006, and it was pushed to the forefront with the presentation of a metanalysis on the subject earlier this year at the **World Congress of Cardiology Conference** (WCC) in Barcelona, which was highly critical of the early claims for DES.

Recent downturns in DES use already indicate that cardiologists in the U.S. are re-evaluating the broad adoption of DES. As shown in **Table 1**, DES utilization in the U.S. has dropped from almost 90% of PCI procedures in the first half of 2006 to an estimated 80% level now. Utilization in regions outside the U.S. has not declined, although the rate of increase in utilization has slowed.

According to some suppliers of DES, such as **Boston Scientific** (Natick, Massachusetts), the No. 2 player worldwide, utilization is likely to rebound in 2007, finishing the year at 85% in the U.S. and continuing to increase slowly elsewhere.

However, that prediction is not shared by all cardiologists. For instance Martin Leon, MD, of **Columbia University Medical Center** (New York), one of the earliest proponents of DES use, has projected that the DES utilization rate in the U.S. could drop to 80% by 2008.

Table 1
Trends in Drug-Eluting Stent Utilization

Country/ Region	Drug-Eluting Stent Market Penetration (percentage of total coronary stent procedures)					2007 Market Size (\$ millions)
	Q4/2003	Q4/2004	Q4/2005	Q4/2006	Q4/2007	
U.S.	61%	86%	87%	80%	80%	2,950
Japan	0%	60%	70%	71%	72%	1,800
International	25%	38%	46%	53%	56%	548

Source: Boston Scientific Annual Analyst Meeting Presentation, Nov. 6, 2006; Cardiovascular Device Update

Cordis (Miami Lakes, Florida), a unit of **Johnson & Johnson** (New Brunswick, New Jersey), the global DES market leader, released the results of its analysis of late stent thrombosis with the Cypher stent in a Nov. 8 webcast, just prior to the start of the AHA conference, showing no excess in the rate of thrombosis for the Cypher compared to BMS when only definite or probable thrombosis incidents are included.

Other analyses included adverse events not definitively shown to be due to a cause other than stent thrombosis within the definition of late stent thrombosis. Nevertheless, it is clear that many cardiologists are re-evaluating their criteria for deciding when to use a drug-eluting stent vs. a bare metal stent.

In STEMI patients, for example, the use of DES provides little added benefit compared to BMS because rates of restenosis in those patients are already quite low (5%-7%) when BMS are used.

DES use is not only more costly but indications are that DES devices also may expose the patient to a long-term risk of thrombosis.

In elective PCI procedures in non-MI patients, there are definite benefits in reduced restenosis rates with DES, but this comes with the added risk of late thrombosis as well as the cost of extended dual anti-platelet therapy, estimated at \$1 billion annually at current levels of DES utilization.

Second-generation DES in position

The situation could change in the future as second-generation devices enter the market designed to reduce or eliminate the drawbacks of existing DES.

As discussed by Patrick Serruys, MD, PhD, of the **Thoraxcenter** (Rotterdam, the Netherlands), a number of devices are showing promise in clinical trials, including the CoStar from **Conor Medsystems** (Menlo Park, California), a company that is slated to be acquired by J&J (see story p. 8); a new version of the absorbable metal stent (AMS) from **Biotronik** (Berlin), designed with drug-eluting reservoirs; the Axxion drug-eluting stent from **Biosensors** (Singapore), employing a bioabsorbable drug-eluting coat-

ing and already in use clinically outside the U.S.; a DES that is dual drug-loaded with heparin and sirolimus from **Saha-janand Medical Technologies** (Gujarat, India); and additional devices from **Sorin Biomedica** (Saluggia, Italy), **Xtent**

(Menlo Park, California) and **Terumo Medical** (Tokyo).

A trend seen in a number of the second-generation devices is the use of bioabsorbable polymers to avoid the adverse inflammatory effects of existing durable polymer coatings. Another approach, exemplified by the Genous R-Stent from **Orbus Neich** (Hong Kong/Hoevelaken, the Netherlands), uses a bioactive coating to attract endothelial cells to the stent surface, in principle producing a non-thrombogenic, biocompatible surface on the stent within 48 hours of implant. That strategy, however, has limitations related to the level of circulating endothelial progenitor cells in the patient's bloodstream.

Devices such as the Conor stent are attractive because of the ability to employ multiple approaches to overcome the problems with first-generation devices, such as using bioabsorbable polymers as well as multiple drugs. An important change in development strategy for next-generation DES is the focus on improving safety and biocompatibility, rather than on further reduction in the rates of restenosis.

New strategies vs. thrombosis

One new tactic for reducing late stent thrombosis events in patients receiving DES implants was described by Matthew Price, MD, of **Scripps Clinic** (La Jolla, California), discussing a study that used the VerifyNow point-of-care assay system from **Accumetrics** (San Diego, California) to determine the responsiveness of stent patients to clopidogrel, the primary anti-platelet drug used to prevent thrombosis.

The standard of care for DES patients now includes three to six months of therapy with clopidogrel and aspirin after the implant procedure. However, a significant percentage of patients, ranging from 5% to 40%, do not respond to clopidogrel, and a similar percentage does not respond to aspirin. Price found that three of the four patients who had a stent thrombosis event were non-responsive to clopidogrel. All four patients were taking clopidogrel at the prescribed dose at the time of thrombosis.

Price said the study shows that non-responsive-

ness to clopidogrel is a cause of stent thrombosis, and he said he believes that a large-scale randomized study should be performed to assess the use of the VerifyNow P2Y12 assay in titrating clopidogrel treatment.

He is also conducting a follow-up study to determine if increasing the dose of clopidogrel in non-responsive patients will reduce the rate of stent thrombosis. Information from anti-platelet drug response testing could also be used along with other patient characteristics to decide whether to use BMS or DES.

Valve repair and reconstruction

A number of presentations at the AHA sessions also covered the latest developments in minimally invasive (MIS) heart valve repair, as well as interventional treatment of heart defects such as PFO, atrial septal defects, and ventricular septal defects.

Thomas Walther, MD, of the **Heart Center** (Leipzig, Germany), described initial experience with the Cribier-Edwards Ascendra prosthetic aortic valve implanted via a minimally invasive transapical approach (TAP-AVI). The device is one of a number of new valves under development by **Edwards Lifesciences** (Irvine, California) that can be implanted using MIS techniques. Walther presented the results of a feasibility study using the device in 34 high-risk patients.

The implant procedures were performed in a hybrid operating room by cardiac surgeons, using a mini-thoracotomy to provide access for the 40 Fr sheath required by the Ascendra device, which has a diameter of 25 mm. The procedure was performed on the beating heart, using extracorporeal circulation in 16 patients.

The pericardial xenograft valve is fixed within a 16 mm-long stainless steel balloon expandable stent. Good valve positioning was achieved in 93% of the patients, with the remainder requiring conversion to open surgery. Total procedure time was six hours.

Twelve patients had mild perivalvular leaks, two had moderate leaks, and one had a severe leak. Although mortality at 30 days was 13.6%, that rate was considered normal, based on the risk profile of the patients treated.

The main contraindication for use of the Ascendra valve is calcification of the native annulus. The surgeons are now advocating that Edwards initiate a randomized controlled trial of the device, and believe that the potential target patient population could be very large.

The existing market for prosthetic heart valves used in treatment of all types of heart valve disorders will exceed \$1 billion world-

wide in 2006, and Edwards estimates that up to 50% of individuals with aortic valve disorders are currently not treated.

John Carroll, MD, **University of Colorado Health Science Center** (Denver), discussed the current status of development of devices for interventional treatment of heart defects such as PFOs, atrial septal defects, and ventricular septal defects. Five companies now market devices for interventional repair of heart defects including **NMT Medical** (Boston), **AGA Medical** (Golden Valley, Minnesota), **W.L. Gore** (Flagstaff, Arizona), **Cardia** (Eagan, Minnesota), and **St. Jude Medical** (St. Paul, Minnesota). In addition, **Cierra** (Redwood City, California) is developing the PFX Closure System, which employs transcatheter delivery of radiofrequency energy to weld heart tissue at the site of a PFO and effect closure.

The potential worldwide patient population for devices used to treat heart defects numbers in the millions, as shown in **Table 2**. More than 20,000 PFO closures have been performed using NMT Medical's CardioSEAL and STARFlex devices. The CardioSEAL price was set at \$5,500 in the U.S. under a Humanitarian Device Exemption (HDE), but the HDE was voluntarily withdrawn recently because actual utilization in the U.S. has surpassed the level of 4,000 patients per year, the maximum allowed for an HDE device.

NMT is developing the BioSTAR, a bioabsorbable porcine collagen PFO closure device comprised of extracellular biomaterial that promotes cell growth and a cobalt metal framework. The biomaterial is replaced by native tissue over a period of about two years after implant, leaving only the metal framework as a permanent implant.

That not only minimizes the potential risk associ-

Table 2
Potential U.S. Patient Population for Percutaneous Heart Defect Repair Devices

Recurrent cryptogenic stroke, transient ischemic attack	250,000 annually in U.S.
Migraine headache with aura	~10% of the adult population in the U.S., Europe and Japan have migraine headache, and ~5% of those have aura, or 4.5 million worldwide
Atrial septal defects, ventricular septal defects	30,000 patients annually in the U.S.

Up to 25% of the population is believed to have a patent foramen ovale that does not fully seal

Source: John Carroll, MD, University of Colorado Health Science Center, Denver, presented at the American Heart Association 2006 Scientific Sessions, Nov. 12-15, 2006, Chicago; NMT Medical.

ated with the presence of any life-long implant, but also leaves open the possibility to perform a percutaneous valve implant procedure in the same patient if that should become needed.

The FDA has recently allowed a change in protocol for the on-going MIST II trial for use of the BioSTAR. The endpoint of the trial was also altered to reduction, rather than complete elimination, of migraine headache. Worldwide sales of the CardioSEAL and STARFlex devices increased 12.8% in 2005 to \$19.3 million.

Target: vulnerable plaque

The detection of vulnerable plaque — or intrarterial plaque that is prone to rupture and cause a myocardial infarct — continues to be a topic of research focus in cardiology and it has attracted significant investment within the medical device industry. The goal is to develop techniques, ideally non-invasive ones, that can not only detect the presence of vulnerable plaques but also can characterize the plaque to allow physicians to decide upon the most appropriate therapy — ranging from PCI with DES implantation to medical and diet/exercise therapy aimed at prevention of rupture at a specific high-risk site, or modifying the lipid content of plaque as a generalized approach to risk reduction.

Targeted molecular imaging is one increasingly promising approach for characterization of vulnerable plaque, as described by Gang Bao, of **Emory University** (Atlanta). Bao described a technique using DNA-targeted nanoparticles for *in vivo* plaque characterization. The particles also carry a toxin on their surface that create micropores in cells, allowing the DNA to penetrate to the cell nucleus and bind to specific molecular targets characteristic of macrophages, cell adhesion, endothelial activation and shear stress, all of which are potential indicators of vulnerable plaque.

Feasibility studies in animals have shown a correlation between expression of cell adhesion molecules by cells in the inner vessel wall and shear stress, which is believed to be a precursor to plaque development. At present, Bao is using a fluorescence quenching method to detect selective binding of the particles. However, magnetic nanoparticles have also been used that could potentially be used for MR imaging of plaque.

Mark Whooley, MD, of **Stanford University** (Stanford, California), also is developing noninvasive MRI techniques for vulnerable plaque detection. Whooley is using multi-functional nanoparticles formed from synthetic polymers and labeled with gadolinium for MR detection. By varying the polymer composition, the particles can be designed to distribute selectively to blood or various tissues such as the

liver. Whooley has selectively imaged injured segments of carotid arteries using MRI.

The sensitivity of the technique is heightened by the enhancement of the gadolinium signal when it is complexed to the polymer. However, refinement of the technique is needed before reliable selective imaging in humans can be achieved.

Nanoparticles get magnetic attraction

Farouc Jaffer, of **Massachusetts General Hospital** (Boston), described the use of dextran-coated magnetic nanoparticles coated with a molecule that specifically binds to activated macrophages, such as are found in vulnerable plaque. The Activated Macrophage Targeted Agent (AMTA) has been used in a clinical study and shown to selectively localize in regions where activated macrophages are present. A clinical trial has been launched to evaluate changes in the distribution and number of activated macrophages in patients treated with statins to reduce vascular inflammation.

Another version of the agent has been labeled with a cell adhesion molecule (VCAM-1) to preferentially image endothelial cells. And still another agent has been developed that targets proteases that are known to be involved in atherogenesis. Reductions in protease activity in vascular tissue have been demonstrated in studies of animals treated with statins.

Jaffer also has developed a new catheter that can be used to perform near-infrared fluorescence imaging that has been used in animal studies to detect regions of protease activity associated with atherosclerotic injury. The goal is to use targeted fluorescence imaging to identify plaques that are likely to cause atherothrombotic complications such as myocardial infarction.

Molecular imaging agents targeting macrophages for vulnerable plaque imaging are under development by early-stage company **NanoScan Imaging** (Landsdale, Pennsylvania). As described by Fabien Hyafil, of **Mt. Sinai School of Medicine** (New York), a targeted CT contrast agent, N1177-iv, is under development by NanoScan that provides image enhancement of atherosclerotic plaques. The iodine-containing agent is given intravenously, and has been shown to specifically target lipid-rich and macrophage-rich plaques, although so far the nature of the macrophage-specific marker has not been determined. The agent is injected intravenously, and after a two-hour waiting period imaging is performed.

According to Hyafil, the ability of N1177-iv to selectively enhance local concentrations of macrophages in CT images of the vessel wall may be due to the effects of macrophage enzymes on the solubility of the agent. N1177 is also being developed for applications in cancer imaging, and has the obvious

Table 3
Potential Number of U.S. Subjects
for Vulnerable Plaque Imaging

Year	Individuals Age 45 and Older in the U.S. with Coronary Heart Disease
2005	13.2 million
2010	14.5 million
2015	15.4 million

In 2002, there were 7.22 million deaths globally from coronary heart disease. Deaths are predicted to rise to 11.1 million by 2020 (World Health Organization).

Source: Nanoscan Imaging, American Heart Association

advantage of not requiring catheterization while still providing a high-resolution image of the arteries.

As shown in **Table 3**, the number of individuals in the U.S. with coronary heart disease who would be candidates for imaging with an agent such as N1177-iv will total more than 14.5 million by 2010, the earliest date targeted by the company for market introduction. The target patient pool is projected to increase to 15.4 million by 2015.

Evaluating plaque density

Shigeki Kimura, MD, of Tsuchiura, Japan, reported results of a study that tracked the correlation of density of plaque imaged via CT with histological analysis of the plaque tissue after it was removed by directional coronary atherectomy. The study evaluated plaques in acute coronary syndrome (ACS) patients as well as in patients without acute coronary syndromes.

As determined by the CT imaging, plaque density was significantly lower in lipid-rich plaques, the plaques believed to be most prone to rupture, compared to fibrous or mildly calcified plaque. More low-density plaque was also found in ACS patients, consistent with the concept that lipid-rich plaques are the ones most likely to rupture and cause a myocardial infarction.

Another approach in the use of CT to non-invasively detect vulnerable plaque was described by Cynthia McCollough of the **Mayo Clinic** (Rochester, Minnesota). In collaboration with **Siemens Medical Solutions** (Malvern, Pennsylvania), McCollough is assessing a new dual-energy scanner that allows discrimination of different metals, particularly iron and calcium, in CT images. Because iron is believed to be present in higher concentrations in microhemorrhagic plaque containing excess blood, identification of regions of high iron content in plaque could allow vulnerable plaques to be detected prior to rupture, but when the risk of rupture is high.


The Siemens scanner used in the study is FDA-cleared for dual-energy imaging, but the software used for iron and calcium discrimination is still a work in progress. So far, McCollough said she has demonstrated the ability to discriminate iron and calcium in model mixtures and is now proceeding with animal studies.

CT is uniquely suited for making some measurements, since it provides the spatial resolution needed to separate the iron signal produced from blood flowing in the vessel versus iron from blood in microhemorrhages in the vessel wall.

More plaque imaging strategies

A number of other technologies were also described at the AHA sessions that are showing promise for detection and analysis of vulnerable plaque, including intravascular ultrasound, intracoronary thermography, and intravascular optical coherence tomography. These technologies, however, all require an invasive catheterization procedure, making them unsuitable for use as a general screening technique. Instead, such techniques would probably be used after a suspect region of plaque had been detected using a non-invasive molecular imaging modality.

Ultimately, a three-stage triage process is likely to emerge that will consist of initial screening using a panel of risk markers analyzed via *in vitro* diagnostic tests, such as a lipid profile, markers of vascular inflammation, and perhaps genetic tests for specific disorders predictive for coronary artery disease, coupled with physiological tests such as blood pressure measurement. Individuals identified at elevated risk in the initial screen would then be evaluated using noninvasive molecular imaging to determine if suspect plaques are present, and their location in the coronary arteries.

If a positive result is obtained via imaging, the next step would be catheterization and inspection of the suspect plaques with a transcatheter modality to confirm the nature of the plaque and decide upon the most appropriate therapy. 

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Commentary

2006 AHA conference a bit more subdued — as well it should be

By DON LONG

CDU Managing Editor

CHICAGO — Associations that target specific diseases are usually optimistic. They have to be. They put themselves on the forefront of conquering the disease they target. They have to be, because they need to raise money to continue the fight. They have to be, to avoid despair.

And the showcases for their optimism are their annual conferences.

That has clearly been the case with the annual Scientific Sessions of the **American Heart Association** (AHA; Dallas) — lots of upbeat reports and public initiatives launched, last year, for instance, the “wear red” effort and an increased focus on heart disease in women; in all years, the rollout of studies indicating advances in therapeutics that treat this No. 1 killer, supporting the feeling that this thing can be conquered.

But the year 2006 AHA Scientific Sessions appeared to be somewhat different, somewhat less optimistic, somehow a bit more toned down.

The reason?

The reason we think is that — as in the most recent balloting in the U.S. — reality breaks through. And in the case of cardiovascular therapy, reality is pointing ever more clearly to the fact that technology doesn’t save lives, technology can only put off man’s final endpoint.

The more subdued tone was struck in one of the first presentations at the AHA meeting by its president, Raymond Gibbons, who appeared to put “the cat on the roof” (one of my favorite uncle’s phrases implying imminent failure, with the next announcement that the cat is deceased, the result of an ugly fall).

Gibbons did this with what appeared to be a clear effort to reduce expectations. Specifically, he emphasized the difficulties that the AHA faces in reaching its rather daunting goal of reducing heart disease by 25% by 2010, that message a possible semaphore indicating the unreachable reality of that goal.

Gibbons called for major overhaul of the U.S. healthcare system and suggested the need for broad national healthcare coverage — not what you usually hear from top drawer medical types (and my uncle, a GP, wouldn’t have been, since he constantly prophe-

sied the horrors of “socialized medicine” in the U.S.).

Gibbons expectation-reducing message was followed by various market-reducing messages during the conference.

Among the most important was a debate focusing on the increasing concerns about drug-eluting stents (DES) vs. bare-metal stents (BMS), with one study underlining what we had heard from a group of cardiovascular surgeons more than two years ago.

The study indicated that yes, DES had demonstrated early-term reduction of restenosis, but the restenosis effect is only delayed. The study found that restenosis following DES use was low early on but then was equivalent to BMS over three years.

(The thrombosis issue with DES, of course, is still shaking out, but a late-November report out of the prestigious Cleveland Clinic will certainly put an even brighter beam on this and probably depress a DES market already trending down.)


Overall, the take-away would seem to be the standard wisdom that the short-term, manufacturer-sponsored trials should be looked at with considerable skepticism.

Still another report is likely one that caused some concern among the interventionalists at the meeting — that after three days following severe heart attack the outcomes for the angioplasty/stenting strategy fail to produce significantly better results than bypass.

And there was still one more study that drew our attention and — if considered in a broad psychological context — should dampen the optimism of those who consider technology a sort of ultimate answer in healthcare. The study reported that a large majority of those implanted with defibrillators, but very clearly declining in their health status and nearing death, refuse to have their ICDs turned off, even though these devices may continue to provide useless shocks and add to the discomfort of dying, often the worst attribute of this end experience.

We can’t help but extrapolate from this — to say that human beings in a technologically sophisticated environment probably have expectations for med-tech that are much too high.

The healthcare industry, of course, promotes this. More and better technology fits the Western world scenarios of continuing improvement via technology and higher profits, with those profits often translating to more R&D, more technology.

One AHA conference with lowered expectations won’t change this, but we can only hope that clinicians will do the right thing and attempt to put a slight brake on their patients’ faith in the healing powers of technology. ————— 

The study found that restenosis following DES use was low early on but then was equivalent to BMS over three years.

J&J bolsters DES via \$1.4B deal for Conor Medsystems

By HOLLAND JOHNSON
CDU Associate Managing Editor

In a bid to expand its pipeline, especially giving itself an edge in the highly competitive drug-eluting stent (DES) market, **Johnson & Johnson** (J&J; New Brunswick, New Jersey) has pulled out its check book and has made a \$1.4 billion all-cash offer for **Conor Medsystems** (Menlo Park, California). J&J, via its **Cordis** (Miami Lakes, Florida) unit, said the acquisition of Conor will provide it with a "new and unique" controlled drug delivery technology. This technology is currently employed on Conor's CoStar stent system, a paclitaxel-eluting cobalt chromium stent with a bioabsorbable polymer.

The CoStar is currently sold outside the U.S., and enrollment in its U.S. pivotal clinical trial has been completed, with the company expecting an approval in late 2007 or early 2008. It received its CE mark in February.

Cordis, whose Cypher sirolimus-eluting system was the first DES to be approved for marketing in the U.S. in April 2003, gains a potentially much quicker pathway to a second-generation product available immediately in Europe and by 2008 in the U.S. Prior to this deal, which still must be cleared by regulators on both sides of the Atlantic, J&J was not expected to have a next-generation DES available in Europe until 2009 and in the U.S. until 2010.

Nicholas Valeriani worldwide chairman, cardiovascular devices and diagnostics at J&J, said during a conference call that Conor's CoStar stent "is unique in its drug delivery mechanism. The design enhances control and direction of drug delivery, enabling a wider range of drug therapies and potentially increasing the range of clinical applications. The technology holds the potential for the delivery of multiple therapeutic agents that may be useful in the treatment of cardiovascular, peripheral vascular and neurovascular disease."

That technology features a design focus on drug delivery, with the CoStar incorporating hundreds of small reservoirs into which drug/polymer combinations can be loaded. That's distinctly different from the other versions of DES on the market, or coming to it in the near future, which universally involve a drug coating on a conventional mesh stent.

The reservoirs on the Conor stent are designed to allow enhanced control of drug release. In addition, the CoStar features bioresorbable polymers absorbed by the body after the drug is released, which in concert with complete drug discharge may solve the

problem of delayed stent thrombosis, an important issue to the medical community with these devices as of late.

Valeriani also said his company believes the acquisition greatly bolsters its DES portfolio, making it "the most comprehensive in the market in terms of stent design, delivery platform, polymer science, drug and drug delivery mechanisms."

The Conor buy received mixed reviews from Wall Street.

"On the one hand, the acquisition adds much-needed and immediate muscle to J&J's drug-eluting stent pipeline," Bank of America analyst Glenn Novarro said in a note. But the lack of long-term data and pending U.S. trial results on Conor's stents add "considerable risk to the deal," he added.

Marshall Gordon, an analyst at Credit Suisse who has an "underperform" rating on J&J, wrote that the acquisition was a "step in the right direction," noting that J&J's drug-eluting stent pipeline is almost non-existent. The big issue, he wrote, is whether an intellectual property (IP) challenge from **Boston Scientific** (Natick, Massachusetts) could delay arrival of the CoStar stent.

Larry Biegelsen, of Prudential Financial, said he believes Boston Scientific stands to lose the most if this deal goes through. He said in a research report that the CoStar "may have safety advantages over the Taxus" and he believes "J&J's resources will improve the chances of Conor prevailing in its IP litigation with Boston Scientific."


Conor stockholders will receive at closing \$33.50 for each outstanding Conor Medsystems share. The \$1.4 billion estimated value of the deal is based on Conor's 42.7 million fully diluted shares outstanding, net of estimated cash. The deal, which still requires Conor Medsystems stockholder approval, is expected to close in 1Q07.

While the CoStar stent is an important device, Conor is not a one-device company. It also is developing a dual-drug DES called the SymBio. The SymBio, currently in a clinical trial called GENESIS, is a pimecrolimus/paclitaxel-eluting coronary stent system. Enrollment in that clinical trial, conducted in the Middle East and Europe, is expected to be completed in late 2006 or early 2007.

The SymBio will be engineered to first release the pimecrolimus drug into the artery to prevent early inflammation, with the paclitaxel then releasing more slowly to have a second impact on later proliferation. The goal will be to develop a stent that targets high-risk patients, such as diabetics. In this strategy, what is left is just the bare metal stent.

J&J CFO Robert Darreta said during the conference call that, upon closing, the company is expected to incur an estimated one-time after-tax charge of about \$600 million, reflecting the write-off of in-

process research and development charges. He said the transaction will be dilutive to 2007 earnings and will be “essentially break-even in 2008.”

The company currently has distribution deals with **Biotronik** (Bulach, Switzerland) and **St. Jude Medical** (St. Paul, Minnesota) in Japan, but Biegelsen said he understands that change of control provisions allow Conor to terminate those agreements. — 

Medtronic makes final filing for Endeavor PMA

As suggested by Johnson & Johnson’s purchase of Conor Medsystems, the major players are lining up for battle in the “second-generation” drug-eluting stent (DES) wars. Another indication is the report last month by **Medtronic** (Minneapolis) that it has filed the fourth and final module of its premarket approval (PMA) application to the FDA for its Endeavor DES. Medtronic’s PMA submission includes safety and efficacy data on about 4,100 patients treated with Endeavor that include follow-up for as long as three years — a total of 27,000 pages, the company says.

Medtronic said the Endeavor PMA “sets a new standard for clinical data submitted to the FDA . . . from the most wide-ranging patient population and for patients with the longest follow-up ever submitted to support the safety and efficacy” of DES.

“We’ve submitted an extremely robust dossier on the Endeavor drug-eluting stent, and we look forward to working with the FDA on an expeditious PMA review,” said Scott Ward, president of the vascular business at Medtronic. He said Endeavor’s “polymer-drug combination [is] specifically designed to reduce restenosis while maintaining a favorable safety profile. We have submitted a PMA that strongly supports the safety and efficacy criteria needed for U.S. approval.”

The Endeavor is CE-marked and commercially available in more than 100 countries.

It is made of a cobalt alloy with a modular architecture designed to enhance deliverability. In addition to being coated with the cytostatic drug, zotarolimus, Endeavor is coated with phosphorylcholine (PC Coating), a biocompatible polymer designed, Medtronic says, “to simulate the outside surface of a red blood cell and mimic the structure of the natural cell membrane, leading to an optimal healing response around the stent following implantation.”

STENTS, stem cells, genes hottest of hot conference talk

By **HOLLAND JOHNSON**
CDU Associate Managing Editor
And **MARK McCARTY**
CDU Washington Editor

WASHINGTON — The 2006 edition of the Transcatheter Cardiovascular Therapeutics conference unfolded in fairly typical fashion, focusing largely on the increasing debates concerning the value of drug-eluting stents and featuring also a variety of new reports on stem cell therapies — and providing a sort of warm-up to the similar debates and presentations to come at the **American Heart Association** (AHA; Dallas) meeting shortly after.

CDU at TCT

Boston Scientific (Natick, Massachusetts) and **Cordis** (Miami Lakes, Florida) were active in presenting their usual studies which, again offering no surprises, served to say “our stent is better than theirs.” Attendees have seen so many of these studies, however, that **Medtronic** — which is poised to enter the DES market in the U.S. this coming year — served to upstage Boston Scientific and Cordis with its report, issued before the start of the TCT meeting, that it was initiating a large-scale clinical trial focusing on DES safety. Medtronic said that its Patient Related Outcomes with Endeavor versus Cypher stenting Trial (PROTECT) will be the largest randomized trial ever conducted to assess key safety measures of two DES devices, comparing its Endeavor zotarolimus-eluting DES — the DES it has positioned for FDA approval — against Cordis’ Cypher.

Primary endpoint for the PROTECT study will be stent thrombosis, with secondary endpoints that include death and non-fatal myocardial infarction and other customary clinical efficacy endpoints, Medtronic said. The study will enroll 8,000 “real-world” patients at 200 clinical centers in Europe and other international markets and follow patients for an additional two years. “Real-world” patients, the company said, refers to patients seen by physicians in everyday clinical practice, including those with complex medical conditions — a designation clearly meant to differentiate vs. more carefully selected trial patients.

“That’s all comers,” Medtronic spokesperson Scott Papillon told *Cardiovascular Device Update*, “the patients who would typically come into a physician’s clinic on an everyday basis.”

While the timing of the trial may appear calculated as piggy-backing on the current DES debate, Papil-

lon insisted that it was only coincidental. "More than a year ago, we started talking to physicians about it," he said. "It's in response to the call for more [long-term] safety [data] but not necessarily tied to the recent activity that everyone is hearing about."

Results of the trial will be watched closely, of course, but no matter what those results are, the study still will be likely to beg a very large question. PROTECT's key terms are "long-term," "safety," and patients who are "real-world," all targeting the current concerns being raised about DES safety.

But the study circles far afield from the major key concerns being raised about DES stents — the need to evaluate DES vs. bare-metal stents (BMS) in long-term trials by an organization other than a DES manufacturer. No matter what degree of rigor is demonstrated in a company-sponsored trial, such a trial will always be shadowed by a certain amount of skepticism.

Asked if Medtronic had concerns that the DES market has peaked and is now in correction mode due to real-life concerns, Papillon acknowledged these as valid issues, but stressed that the problems are with the first-generation stents. "We think that Endeavor as the next-generation stent offers some answers to that," he said. Among the improvements that he cited for Endeavor over its older brethren include a polymer/drug combo with excellent safety data thus far.

The Endeavor did fail to meet its primary endpoint in a study against Cypher last year. In ENDEAVOR III, the Endeavor stent failed to exhibit non-inferiority in comparison of late-lumen loss. The 282 patients treated with Endeavor had an average in-segment late loss of 0.34 mm at eight months compared to 0.13 mm among the 94 Cypher-treated patients. That 0.21 mm difference, however, was just 0.01 mm more than the trial's predetermined non-inferiority margin of difference.

In response, Papillon said that the late-loss data was determined as not applicable and that late loss has not been shown to lead to adverse clinical outcomes. He noted that Endeavor was "at least as good as the Cypher" in the secondary endpoints and that safety was not studied in ENDEAVOR III.

A stiffer headwind coming?

Whatever the high hopes Medtronic has for ENDEAVOR, the company — and any others attempting to come on line with DES or DES-type combinations of drugs and devices — may face a somewhat stiffer headwind at the FDA and perhaps a longer review process. Its panel and reviewers are going to be asking many more and much tougher questions than Cordis and Boston Scientific had to deal with — or face some heavy outside criticism from those already ready and poised to bash the FDA as having not enough concern for safety. The data required will probably be somewhat longer-term, and

there will certainly be a demand for very much more post-marketing data and surveillance.

Stem cells — 'too much controversy'

Besides the emphasis on the DES vs. BMS debate, the 2006 TCT also featured the growing drumbeat of stem cell therapy studies found in the cardiovascular venue, a research emphasis that continues aggressive percolation in the research arenas but with little evidence of breaking into the commercial and profit-producing venues very soon.

Tim Henry, MD, an interventional cardiologist at the **Minneapolis Heart Institute** (Minnesota), gave an overview of what he considered to be the current state of stem cell research targeting congestive heart failure and other diseases. "Right now, there's too much controversy and, on the other hand, too much hype" surrounding this research, Henry said. He said that the current spate of controversies is focused on a particular kind of stem cell, which he termed "the wrong question," adding that there are a number of stem cell types in the adult human body, all having at least some therapeutic potential. The first question researchers should ask, he said, is "what condition am I trying to treat?"

Henry said that the ability of stem cells to release needed biochemicals to nearby cells, commonly referred to as a paracrine mechanism, is probably as vital a part of their ability to repair organs as anything else. However, he predicted that in the future, "stem cells could be used as couriers to deliver gene therapy." As for diseased hearts, there are "really not a lot of hard data" for this, he said.

One of the studies referred to by Henry appeared in the September 2004 edition of *Circulation*, by Emerson Perin, MD, director of new cardiovascular interventional technology at the **Texas Heart Institute** (Houston). It described the injection of a patient's own bone marrow mononuclear cells in an effort to treat ischemic cardiomyopathy. The authors acknowledge, however, that they do not know which of the mononuclear stem cells found in the bone marrow are responsible for some of the observed ameliorative effect on ischemic myocardium. What may be considered the "usual suspects" of this category include mesenchymal stem cells, stem cells that are progenitors of hematopoietic and endothelial cells, and those stem cells responsible for generating various lymphocytes. They say that the study demonstrated safety by virtue of having triggered no immune response and the results indicate statistically significant improvement in exercise capacity and reduced symptoms of angina. On the other hand, the trial enrolled only 23 patients, nine of whom were controls.

Henry briefly discussed the recently completed Phase I trial for Provacel, made by **Osiris Pharmaceuticals** (Baltimore), intended to treat myocardial infar-

tion by means of mesenchymal stem cells. In the animal models, the mesenchymals migrated to the heart by homing in on the source of markers of inflammation. But the cells in the Provacel trial will follow inflammation markers to other parts of the body. Lacking any biological trail, the mesenchymal cells head for the bone marrow, essentially going home if there is no work to be done. Henry said that this early work “absolutely does not” prove efficacy, but he noted that the trial made use of allogeneic cells, raising the possibility of “one healthy donor” donating stem cells to many others — “a huge step forward.”

Genes and the ‘gamut’ of cells

Nicolas Chronos, chief scientific officer at the **American Cardiovascular Research Institute** (Atlanta), outlined the current state of gene research into heart disease, noting up front that “a whole gamut of cells are involved” in the inflammation leading to atherosclerosis,” thus offering a range of potential tools, but also requiring a wide range of expensive and time-consuming research. At present, reduction of low-density lipoprotein (LDL) is really the mainstay of clinical practice for cardiologists, and that as things stand, “we’re treating the end stage” of atherosclerosis, Chronos said. Gene therapy holds out hope of intervening before a heart becomes heavily diseased, but some research seems geared to bypassing genes altogether.

“We can think of gene therapy as just another way of delivering proteins,” said Chronos, hinting that proteomics may move past genomics as the most promising area of research. One of the confounders of any such research, he said, is that patients who have been treated for various heart diseases “have a very, very high incidence of the placebo effect.”

One approach to fending off atherosclerosis, Chronos said, might be to target a gene such as hypoxia-inducible factor (HIF 1), which he said embodies “the cell’s ability to measure the latent oxygen in the environment” and correlates with the onset of atherosclerosis. HIF 1, he said, can induce angiogenesis and could play an important role in treating heart disease.

At present, **Genzyme** (Cambridge, Massachusetts) has an HIF 1 product in Phase II clinical trials to deal with vascular disease in the lower extremities, and the **National Cancer Institute** is recruiting for a Phase I trial to see if topotecan hydrochloride can suppress HIF 1 and hence cut off the blood supply in an unspecified group of cancerous tumors. These efforts, however, will not likely result in very near-term clinical application, he said.

As something more promising, Chronos discussed research at the **University of Pennsylvania School of Medicine** (Philadelphia) involving intravenous delivery of an adenoviral source of human

apolipoprotein E (apoE) in apoE-deficient mice to see if this xenogeneic source might prevent atherosclerosis. The research team, headed by Ken Kitajima, MD, found that “extensive atherosclerosis was present in the thoracic aortas and aortic roots” of the controls after one year of treatment but “completely prevented” in the experimental group.

Topol to head new institute


Among one of the more intriguing reports out of the TCT meeting was that Eric Topol, MD, former chairman of the department of cardiovascular medicine at the **Cleveland Clinic** (Cleveland), was named to head a new Translational Science Institute and Genomic Medicine Program for **Scripps Health** (San Diego) healthcare system. Topol left the Cleveland Clinic last year in what was considered the fall-out of his failed effort to be named CEO of the clinic. This departure was also widely seen as the result of conflicts with Toby Cosgrove, MD, who did win the clinic CEO position. Thus, the appointment of Topol to the new institute provides him a new platform for his work in genetic-related disorders.

Chris Van Gorder, president/CEO of Scripps, said that Topol is “the first of many physician/scientists we hope to bring to Scripps in other clinical specialties. Just as Dr. Topol took the Cleveland Clinic to the No. 1 heart program in the nation, we know his contributions will help Scripps realize its vision of becoming the destination heart program for the West Coast.”

Scripps in October reported a major expansion of its clinical research program, led by academic oncologist and clinical researcher Brian Issell, MD. Topol and Issell will work together to expand Scripps’ clinical research.

“Scripps has everything it needs to be a world leader in cardiovascular medicine, genomics and translational science,” Topol said. “The excellent clinical reputation of Scripps Health coupled with its longstanding relationship with The Scripps Research Institute, the genetic diversity of the San Diego population and its high concentration of exceptional biotechnology creates the ideal environment to develop a leading genomics and translational science program.”

Topol is also program director for the Specialized Center of Clinically Oriented Research on the molecular determinants of coronary artery disease, supported by an \$18 million grant from the **National Institutes of Health**, and a professor of genetics at the School of Medicine of **Case Western Reserve University** (Cleveland).

His work in the genomics of coronary disease led to the discovery of the first autosomal dominant mutation-inducing coronary disease and heart attack, bringing him a variety of awards. ————— 

One-kind-makes-all may be stem cell pathway to heart

By ANETTE BREINDL
CDU Science Editor

Several studies in recent and upcoming issues of *Cell* and *Developmental Cell*, respectively, have identified cardiac stem cells that give rise to an unexpected combination of daughter cells. Taken together, the reports challenge current notions of how the heart develops, and might provide insights for regenerative medicine.

The heart consists of three main types of tissue: cardiac muscle, which does the beating grunt work; vascular smooth muscle, which lines the heart's blood vessels; and endothelial cells, which line the heart itself, as they do with the rest of the circulatory system. Currently, most researchers say that those tissue types derive from distinct embryonic stem cells.

But two papers to be published in the Dec. 15, 2006, issue of *Cell* challenge that notion.

The first paper, by researchers from **Massachusetts General Hospital** and **Harvard Medical School** (Boston), the **University of California at San Diego**, and the **Technical University of Munich** (Munich, Germany), reported that in lineage tracing studies, stem cells expressing the marker *isl1* gave rise to not only cardiac muscle but also smooth muscle, endothelial, pacemaker, and other nonmuscle cell lineages.

Single cell 'surprise'

"It's a surprise that a single cell can give rise to all of these tissues and structures in the heart," said senior author Kenneth Chien, professor of basic science at Massachusetts General Hospital and Harvard Medical School. "The heart may look more like blood than we thought."

In the second paper, researchers from **Children's Hospital, Beth Israel-Deaconess Medical Center**, the **Dana-Farber Cancer Institute**, and **Massachusetts General Hospital** (all Boston), the **University of Southern California** (Los Angeles) and the **Harvard Stem Cell Institute** (Cambridge, Massachusetts), isolated cells from a mouse embryo that expressed a cardiac-specific gene, called *Nkx2.5*.

While the *Nkx2.5* cells spontaneously differentiated primarily into cardiac muscle cells and conduction system cells, some of the precursor cells unexpectedly turned into smooth muscle cells.

The team isolated *Nkx2.5* cells derived from embryonic stem cells and found that some of the cells also expressed a second gene, *c-kit*. It was the *c-kit* *Nkx2.5* cells that had the ability to expand and pro-

duce both cardiac muscle and smooth muscle cells from a single cell. The team confirmed that finding by isolating cells in which both genes were active and demonstrating their ability to form both heart muscle types *in vivo*.

In discussion of their work, the authors wrote that "in summary, we have established the existence of a common myogenic precursor cell that gives rise to both myocardial and smooth muscle lineages," adding that the findings "reveal a hierarchy for myogenic differentiation *in vivo* and suggest a new developmental paradigm for cardiogenesis, where a single multipotent progenitor cell gives rise to cells of diverse lineages within the heart."


Both *Cell* papers come on the heels of a November *Developmental Cell* paper, in which researchers from the **Mount Sinai School of Medicine** (New York) isolated a stem cell that could produce all three types of heart tissue by using another molecular marker, *Flk-1*.

'Parental' relationship unclear

The papers have worked out the progeny of their respective stem cells, but the relationship of the parents to each other still is unclear. Chien and colleagues isolated stem cells that are the progenitors of the heart's right chambers, while the cells of the team led by Stuart Orkin of Children's Hospital were slated to become part of the left chambers. Orkin's *c-kit* and *Nkx2.5* expressing cells may be daughters of the *Isl1* expressing cells, but the two stem cell types may also be unrelated; both labs are currently working on determining the relationship, or not, between the two stem cells.

While the work is basic research, its implications might be useful in the clinic.

Chien said that "embryonic stem cells are difficult to use for heart regeneration because of the danger of teratomas," which are cancers that result from the uncontrolled growth of embryonic stem cells.

"If we can get around that threat by cloning master cardiovascular stem cells that would be a major advance." 

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International report

Initial implants in Sorin dual-chamber ICD OPTION trial

A CDU Staff Report

The Cardiac Rhythm Management group of **Sorin Group** (Milan, Italy) reported the initiation of the Optimal Antitachycardia Therapy in ICD Patients without Pacing Indication (OPTION) clinical study in Europe. The study objective is to demonstrate that implantable dual-chamber cardioverter defibrillators (ICDs) have greater efficacy than single-chamber ICDs in reducing inappropriate shock delivery and have the same efficacy in reducing all-cause patient mortality and hospitalizations due to cardiovascular events.

OPTION, multi-center and two-armed, aims to demonstrate that patients implanted with dual-chamber ICDs incorporating features such as optimal dual-chamber arrhythmia detection, a pacing mode that minimizes ventricular pacing and a slow ventricular tachycardia zone, have better outcomes in terms of inappropriate shock delivery, patient mortality and hospitalizations than patients with single-chamber devices.

The first patients enrolled in the OPTION in Germany, Portugal and Italy were implanted with Sorin's Ovatio dual-chamber ICDs featuring the PARAD+ arrhythmia detection algorithm, AAIsafeR mode that limits ventricular pacing and a slow ventricular tachyarrhythmia (VT) zone. Patients included in the study are randomized to either single-chamber ICD therapy following standard clinical practice with an active monitoring zone to allow ventricular arrhythmia documentation, or to dual-chamber detection and therapy in the slow VT zone with AAIsafeR switched on.

"We are confident that OPTION will significantly help us assess whether dual-chamber ICD therapy gives clinical benefit to patients without a pacing indication," said Christof Kolb, MD, of **Deutsches Herzzentrum** (Munich, Germany), the principal study investigator. "Ovatio DR innovative features and the design of the trial will enable us to investigate the impact of ICD therapy on the full range of ventricular tachyarrhythmias, including slow VTs, in combination with pacing backup in patients with impaired left ventricular function to avoid unnecessary ventricular stimulation. We also expect that the results of OPTION will help us in better selecting ICD candidates."

Another objective of the study is to determine how to best identify patients who could benefit from ICD therapy using Sorin Group's "T-variability" risk

stratification method, a noninvasive Holter-based test that analyzes micro-volt variations that are linked to the development of life-threatening tachyarrhythmias.

The OPTION study will enroll 450 patients in Europe, Canada and the U.S. Interim results will be published every 12 months. A follow-up phase of 27 months is scheduled after enrollment to allow monitoring of the development of atrial fibrillation and congestive heart failure.

Abiomed, Medix Japan in distribution pact

Abiomed (Danvers, Massachusetts) reported a five-year distribution agreement with **Medix Japan** (Tokyo), a company that distributes cardiac assist devices in that country. Building on its eight-year relationship with Abiomed, Medix will initiate clinical trials in Japan during Abiomed's FY08. The agreement provides for distribution of Abiomed's AB5000 and Impella products and includes a minimum purchase of Impella products of \$11 million within the first 18 months following Impella regulatory approvals in Japan. The balance of the purchase commitment for Abiomed's other products begins in Abiomed's 1Q08.

Yasu Matsuoaka, president of Medix, said. "We believe that this technology will have a profound effect on patient care and are totally committed to working with our government officials and the Abiomed team to bring these products to the Japanese market as rapidly as possible."

Michael Minogue, president/CEO of Abiomed, said, "Japan represents a sizeable market for our recovery technologies with a population of approximately 127 million, 600 open heart hospitals and 1,800 catheterization labs. Heart recovery is one of the main priorities in Japan and their physicians often provide some of the most elaborate evidence-based scientific publications in the world. We have found a valuable partner with Medix and are excited for the future," Minogue said.

Abiomed makes the AB5000 Circulatory Support System and the BVS 5000 Biventricular Support System for the temporary support of all patients with failing but potentially recoverable hearts. In Europe, Abiomed offers the minimally invasive Impella Circulatory Support System under CE mark approval. The Impella 5.0 and 2.5 are investigational devices limited to investigational use in the U.S.

Lombard wins supplemental IDE

Lombard Medical Technologies (Oxfordshire, UK) reported receiving conditional FDA approval for its supplemental Investigational Device Exemption (IDE-S) for its pivotal U.S. clinical trial of the Aorfix endovascular stent graft in the treatment of abdominal aortic aneurysms (AAAs). The company said it

originally envisioned the trial as having two endovascular arms, one for aneurysms with neck angulations of up to 60 degrees (low- or moderate-angle cases) and one for aneurysms with neck angulations of between 60 degrees and 90 degrees (high-angle cases), as well as an open surgery control arm. But the FDA has provisionally accepted arguments in the supplemental IDE submission to have a single endovascular arm in which each center could recruit patients with any neck angle up to 90 degrees following an initial recruitment of five low/moderate angle cases.

Lombard said this change in trial design allows a reduction of the number of cases to be performed from 385 to 210, shortening the time required to recruit patients into the trial. It said that since the centers cannot enroll high-angle cases (for which there is no licensed endovascular treatment option) until they have completed five low- or moderate-angle cases, there now is an incentive for them to recruit low- or moderate-angle cases quickly.

The IDE-S also allows Lombard Medical to use the improved version of Aorfix launched in Europe in April in the trials. The company said that product is "much preferred" by physicians due to its greater flexibility, longer shelf life and increased visibility under X-ray.

Alistair Taylor, executive chairman of Lombard, said that the changes "will benefit from earlier access, albeit in a trial, to a device that can be used in high angle cases for which there is currently no approved endovascular treatment option in the U.S. We believe that this, along with access to our improved device, will have a significant impact on recruitment rates resulting in Aorfix entering the important U.S. market earlier than previously anticipated."

Lombard's latest project is to develop a coated stent that encourages local self-repair of blood vessels. This involves attaching stem cell-derived endovascular cells to Lombard's programmable polymer coating on the stent surface, which will allow the human body to promote controlled vascular repair and heal the damaged coronary artery vessel wall itself.

Elbit unit wins FDA OK for StemEx study

Elbit Medical Imaging (Tel Aviv, Israel) reported that its subsidiary, **Gamida Cell**, in which EMI holds a 25% stake, has reached an agreement with the FDA for a special protocol assessment (SPA) for the design of a pivotal registration study of StemEx for the treatment of hematological malignancies. Gamida Cell is developing StemEx in a joint venture with **Teva Pharmaceutical Industries** (Jerusalem).

StemEx is composed of *ex vivo* expanded cord blood stem/progenitor cells which are transplanted in combination with non-expanded cells from the same cord blood unit. Stem cell transplantation is a treatment for high-risk hematological malignancies. It

is thought to provide an alternative source of stem cells for these patients by enabling the use of cord blood for transplantation.

StemEx was granted an FDA Orphan Drug designation in March 2005.

Gamida Cell reports a product in "advanced" pre-clinical development for the treatment of heart disease.

SunTech opens Hong Kong office

SunTech Medical (Research Triangle Park, North Carolina), a developer of motion-tolerant, non-invasive blood pressure monitoring technology, has opened a new sales and service office in the Bank of China Tower, Hong Kong. Anthony Nixon, director of Asia/Pacific sales, has relocated from the company's office in Oxford, UK, to the Hong Kong branch.

Nixon said the company's presence in Hong Kong "will enhance our ability to provide service and support to customers throughout East Asia, Southeast Asia and the Indian subcontinent."

SunTech offers products for 24-hour ambulatory blood pressure monitoring, cardiac stress BP monitoring, customizable OEM BP modules and blood pressure cuffs. SunTech is a subsidiary of **SunTech Medical Group** (Oxford, UK), a holding company focused on medical diagnostics.

Angiotech seeks CE mark for Vascular Wrap

Angiotech Pharmaceuticals (Vancouver, British Columbia), a specialty medical device and pharmaceutical company, reported that it has submitted an application for a CE Mark for its Vascular Wrap paclitaxel-eluting mesh/ePTFE vascular graft combination product on the strength of the results from its European first-in-man study. William Hunter, MD, president/CEO of Angiotech, said, "With the acquisition of the vascular graft product line from **Edwards Lifesciences** [Irvine, California] last year, as well as the acquisition this year of **American Medical Instruments** [New Bedford, Massachusetts], we believe we are well positioned to capitalize on and economically benefit from this potentially category-defining product.

"We believe the market potential for our Vascular Wrap product could be significant. With the results from the two-year European study and our upcoming trials in AV Access in the UK and U.S., we believe that we have the potential to build a significant vascular franchise."

The two-year trial produced data indicating that treatment with the Vascular Wrap reduced the overall incidence of leg amputation and prolonged limb retention time in patients suffering from late stage peripheral arterial disease who underwent bypass surgery. For the patients that required an amputation during the study period, the mean interval to amputation for patients treated with the Vascular Wrap was

156 days — more than double the mean interval to amputation for the control, which was 76 days, and it appeared to be well tolerated, with no adverse events related to the use of the product.

The Vascular Wrap consists of both the ePTFE graft and the Vascular Wrap paclitaxel-eluting mesh. The Vascular Wrap component is a biodegradable mesh implant incorporating Angiotech's paclitaxel technology in a biomaterial with the goal of mitigating scar formation caused by abnormal blood flow thereby potentially enhancing graft patency rates in AV-access patients as well as in peripheral bypass procedures.

The Vascular Wrap in combination with an ePTFE graft was compared to a control group of patients that received standard of care — an ePTFE graft alone.

Some key findings:

- Adverse events (AE) leading to death occurred in a lower percentage of treated subjects (11%, 8/71), than in controls (18%, 7/38).
- The incidences of adverse events and serious adverse events were comparable in treated (graft with Vascular Wrap) and control (graft alone) groups.
- No adverse events were considered by the investigators to be related to the use of the Vascular Wrap.
- Overall, the action taken to resolve AEs was similar for the two groups, and the outcomes were comparable.
- When comparing the treatment arm relative to the control, the Vascular Wrap maintained the mean diameter of the distal anastomosis during the 24 month trial compared to a decrease in mean diameter in the control arm. This reached statistical significance ($p = 0.0333$).

The single-blind study enrolled a total of 109 patients at nine clinical centers in Europe as well as the Dutch Antilles and randomized patients with peripheral vascular disease in a 2:1 fashion. The treatment arm enrolled patients with a synthetic bypass graft plus the Vascular Wrap paclitaxel-eluting mesh, and the control arm enrolled patients with a synthetic bypass graft alone.

The success of grafting to restore blood flow depends on inflow and outflow of the graft. The trial results show trends that suggest that the use of the Vascular Wrap in these procedures may increase the success rates of vascular graft surgery.

TopSpin Medical raises \$11 million

TopSpin Medical (Tel Aviv, Israel) reported raising \$11 million in convertible bonds from institutional investors on the Tel Aviv stock exchange.

TopSpin, which has developed a technology platform designed to enable MRI to be conducted with no external magnets, says that the ability to perform high-resolution local MRI with no external

magnets is “a breakthrough in medical imaging as it enables the extension of MRI technology to a wide range of applications, in which conventional MRI cannot get to the required resolution or is simply too bulky and expensive.”

The primary application is high-resolution imaging of coronary artery walls during cardiac catheterization by a single-use, IntraVascular MRI (IVMRI) catheter. The IVMRI catheter has demonstrated accurate characterization of the lipid composition of atherosclerotic plaque — the most important factor in determining plaque instability.

TopSpin has successfully completed its first-in-man (FIM) clinical trial, which, the company anticipates, would allow it to obtain a CE mark for the IVMRI system by the end of 2006. An additional clinical study is now ongoing in more than 10 centers in Europe, Israel and the U.S. To date, about 100 patients have been enrolled in TopSpin's studies with good safety and performance results. The company said it plans to use the data to obtain FDA market clearance, which is expected by mid-2007.

“The \$11 million raised will allow us to launch our IVMRI catheter in Europe and in the U.S., while continuing to invest in an extensive post-marketing clinical program that would help build our market,” said Erez Golan, TopSpin's president/CEO.

Enrollment completed in LeMaitre trial


LeMaitre Vascular (Burlington, Massachusetts) reported the enrollment of the 30th and final patient in the EndoFit Thoracic Stent Graft Clinical Study in that country.

The company said the objective of the study is to obtain data in support of approval of the EndoFit Thoracic Stent Graft from the Chinese State FDA (SFDA). Completion of patient enrollment marks the start of a six-month follow-up and observation period.

George LeMaitre, president/CEO and chairman, called the enrollment figure “a key regulatory milestone in this rapidly emerging endovascular device market.”

The EndoFit Thoracic Stent Graft is used to treat aortic aneurysms. The device's encapsulated design prevents its stents from contacting the bloodstream or the vessel wall, thus allowing a wider range of stent graft sizes, including tapered and custom grafts, to fit a wider range of patient anatomies than many competing products.

Dr. Weiguo Fu, director of the endovascular department at **China Fudan University Zhongshan Hospital**, said, “The radial force of the proximal end of the EndoFit Thoracic Stent Graft seems superior, as we have not seen any migration post-implantation.”

The EndoFit Thoracic Stent Graft is sold in the European Union and a small number of other foreign jurisdictions. ————— 

Acquisitions

• The FDA has approved the NexStent Carotid and Monorail Delivery System for carotid artery disease patients who are at high risk for surgery — that approval taking **Boston Scientific** (Natick, Massachusetts) within weeks of acquiring **EndoTex Interventional Systems** (Cupertino, California). The NexStent is manufactured by EndoTex and has been distributed exclusively by Boston Scientific outside the U.S. since it received the CE mark in 2005. Boston Scientific said it will acquire EndoTex within 90 days under the companies' existing agreements. EndoTex said that its FilterWire EZ Embolic Protection System, which was studied together with the NexStent Carotid Stent in the CABERNET clinical trial, is still pending 510(k) clearance by the FDA. Paul Edwards, a spokesman for EndoTex, told *Cardiovascular Device Update* that the approval of NexStent, the company's core product, was a primary goal for EndoTex and key to moving the company closer to its acquisition by the big interventional technology company. "This is Boston Scientific's opportunity to go out into the U.S. market and talk about carotid stenting," Edwards said. "We're providing them with access to the U.S. market" in this particular sector. The NexStent is a laser-cut, nitinol stent with a rolled sheet design enabling one stent size to adapt to multiple diameters in tapered or non-tapered vessel configurations, according to the company. This "self-sizing" feature is designed to provide adaptability when treating lesions in the carotid arteries, and its closed-cell configuration is designed to increase lesion coverage and provide a smooth inner lumen to help facilitate delivery and retrieval of ancillary devices. The NexStent Carotid Stent is intended "to provide a low profile option for physicians who want a high degree of flexibility and plaque stabilization," the company said in a statement. Joseph Tartaglia, president/CEO of EndoTex, said approval of the NexStent was based on results of the CABERNET trial. Boston Scientific offers accessories for the stenting system, including the Sterling Monorail PTA Balloon Dilation Catheter, Thruway Peripheral Guide Wire, Amplatz Super Stiff Guide Wire, the Mach 1 Peripheral Guide Catheter, and Imager II Angiographic Catheter. Since they are located on the sides of the neck, the carotids are the main conduit through which blood flows from heart to brain, and plaque formation in them can impede blood flow, increasing the risk of stroke. Until recently, the primary option for opening these vessels was carotid endarterectomy, a procedure involving a vertical incision in the neck and artery and removal of the plaque. Carotid artery stenting, a less-invasive procedure, involves guiding a stent-bearing catheter

to the carotids, at the site of the blockage, where it expands and forces the walls of the arteries open, restoring the blood flow. "This is an innovative stenting system that interventionalists in the U.S. have been waiting for," said Subbarao Myla, MD, of **Hoag Memorial Hospital** (Newport Beach, California), and co-principal investigator of the CABERNET trial. "Study results demonstrate excellent outcomes at one month — when there is the greatest risk of procedure-related stroke — through one year in patients with a wide range of lesions and vessel anatomy." Boston Scientific first invested in EndoTex in July 2001, with an option to buy the company, which specializes in carotid stent technology. The FDA approval of NexStent and Boston Scientific's pending acquisition of EndoTex could help the company end the year on a more positive note than it started on in January when it was issued a rare warning letter by the FDA. The letter was only the third such corporate-wide warning ever issued to a medical device company, the agency said. The letter cited company management for failing to properly track complaints concerning certain products, including its Taxus stent, as well as Vaxcel catheters, Leveen needle electrodes and the Enteryx device used in surgery to treat acid reflux. It said that Boston Scientific also failed to notify it about such complaints, citing three company facilities. The FDA's concerns have served to block the agency's approval of new products from the company. The letter came just one day after Boston Scientific sealed its purchase of **Guidant** (Indianapolis) for about \$27.2 billion, outbidding **Johnson & Johnson** (New Brunswick, New Jersey).

• **Viasys Healthcare** (Conshohocken, Pennsylvania) acquired the assets of **BioBeat Medical** (Kadima, Israel) for about \$4.5 million. The acquired products are the Sonara and Sonara/tek which incorporate advanced digital Transcranial Doppler (TCD) technology. TCD is a non-invasive method of measuring blood flow velocities in the arteries of the brain using ultrasound Doppler technology. "We believe this acquisition represents a significant addition of neurovascular technology to the NeuroCare portfolio," said Lori Cross, group president of Viasys NeuroCare. "This acquisition provides our neurovascular business with advanced TCD tools for diagnosis, monitoring and treatment of cerebrovascular disease, especially stroke," Cross said. The Sonara and Sonara/tek will be launched this month in Europe and will be launched in the U.S. market immediately upon FDA 510(k) clearance, which is pending. Viasys is focused on respiratory, neurology, medical disposable and orthopedic products.

Business Developments

Medtronic to spin its AED business

In a move that may alter the dynamics of the automated external defibrillator (AED) market, **Medtronic** (Minneapolis) has unveiled a plan to send its 1998 acquisition, **Physio-Control** (Redmond, Washington), back out on its own sometime in the first half of the company's fiscal 2008. The spin-off, said Art Collins, Medtronic CEO and chairman, is being made because Physio-Control "is not central to our long-term strategic business."

In a conference call, Collins described the spin-off of its division making AEDs as a win-win situation. He said, "[w]e believe this transaction . . . will allow Physio to renew its focus, while allowing Medtronic to focus" on opportunities that align better with its strategic aims. Those aims, he said, include pursuing growth in the mid-teens.

Medtronic picked up the firm for \$538 million in stock in June of 1998. The company, which operated as Medtronic's Emergency Response Systems division, will continue operations with its headquarters in Redmond, Washington, the location of its headquarters prior to the Medtronic buy-out.

Gary Ellis, Medtronic's CFO, said the move will offer Physio-Control "new levels of investment and operating flexibility" and that for the next six to nine months, the spin-off will have "no impact on current fiscal year per-share guidance, . . . but our fiscal '08 guidance" will be affected. Ellis said that transaction-related costs "are not expected to be significant."

Physio-Control has not suffered under the Medtronic umbrella. It had \$178 million in sales in 1998 and should ring up about \$450 million in fiscal 2007. However, Ellis suggested that Medtronic's flagging interest in Physio-Control's product line might eventually have resulted in under-investment.

Brian Webster, who will assume the title of CEO of the new Physio-Control, said that the emergence from the Medtronic umbrella represents "a chance to assume all control of our operations and our strategic direction." He said that the firm as an independent entity "will continue to provide the state-of-the-art technology and the world class service our customers have come to expect."

Medtronic picked up the smaller unit in a pooling-of-interests stock transaction that netted Physio shareholders \$27.50 in Medtronic stock for each share of Physio-Control. However, the subsequent explo-

sion of sales of implantable defibrillators and coronary stents pushed AEDs into the background, despite the fact that Physio-Control grew its revenue stream at about the anticipated rate of 8% to 12% a year.

"Medtronic is a very different business" than it was in 1998, Collins said, adding that the resources that Physio-Control needs to grow may not be available from the Medtronic checkbook. Medtronic said it will pump the freed-up financial resources into other units. Implantable cardioverter defibrillators are still an "attractive growth platform" as are several other technologies, Collins stated. The firm's drug-eluting stent (DES) business will benefit from the sale, too, "but not exclusively," he said, a rather clear reference to the potential roll-out of the company's Endeavor DES in the U.S., which it hopes to see happen by the second half of next year.

Collins characterized Physio-Control as "an attractive business, but perhaps more so as an independent company." He said that a problem with attempting to build and promote both AEDs and ICDS is that "[t]here are not enough tangible operating synergies to make business sense." They are mechanically very different and, for Medtronic, made in different locations. "The selling and servicing requirements are different," and even sales to hospitals are not that closely tied, he said.

Ellis also noted that Medtronic was never able to create any sales synergies between the products in the hospital market since AEDs are a capital equipment purchase while ICDS are purchased as therapeutic devices. "There really is very little synergy on the [sales] call side," Ellis observed.

Latitude System FDA-approved

The FDA has approved what **Boston Scientific** (Natick, Massachusetts) calls the first remote monitoring system to provide clinicians with direct device data integration capability into the Centricity Electronic Medical Record (EMR) from **GE Healthcare** (Waukesha, Wisconsin). The companies recently reported the first integration of remote device information direct to EMRs. The FDA approved the Latitude Patient Management software — a remote monitoring system for cardiac device patients — with integration capabilities into the Centricity EMR.

The system is for patients implanted with a Con-tak Renewal 3RF device, a combination pacemaker and defibrillator with radio frequency, Dave Knutson, a Boston Scientific spokesman, told *Cardiovascular Device Update*. While the patient is sleeping at night another device — the communicator, which Knutson said resembles a Caller ID box with a short antenna — sits near the bed and collects vital information from the patient's implanted device and sends it to the doctor's office through the phone line

to a secure web site. A doctor or nurse accesses the web site to check the patient's device and vital signs. "For the patient it offers peace of mind and daily assurance that their device is working every single day," Knutson told *CDU*.

Boston Scientific gave demonstrations of its Latitude Patient Management System at the meeting of the **American Heart Association** (AHA; Dallas) in mid-November, but Knutson said the company will not be giving formal presentations or releasing any clinical results yet. He anticipates that next year's AHA conference will likely include a presentation on the device.

Knutson said the system also reduces unscheduled doctor's visits because if a patient thinks something might be wrong he or she can call the doctor who can "simply go online and say, 'you know what, your device is working perfectly — why don't you wait and come in tomorrow for your scheduled visit.'"

Another feature of the system, he said, is the device's ability to send the doctor yellow and red alerts. Yellow might tell the doctor, for example, that the device's battery is getting low and red normally indicates something is wrong with the device or the patient. **Guidant** (Indianapolis) received FDA approval for the Latitude Communicator and secure data storage system in September 2005.

Being able to use the system with GE's Centricity EMR provides another benefit for the physician, Knutson said. "Now our doctor who logs on not only gets a device status and the patient's status, but can get the patient's whole medical history," Knutson said.

Vishal Wanchoo, president/CEO of **GE Healthcare Integrated IT Solutions**, called the GE/Boston Scientific collaboration a "major stepping stone" in GE's effort to provide a comprehensive patient record across the continuum of care. "The ability to collect patient data remotely using Latitude technology and integrating that data, along with historical medical information, within the patient's electronic medical record should empower physicians to make more accurate decisions at the point of care," Wanchoo said. The Latitude system could cost up to \$33,000, Knutson said, which includes the implanted device, the communicator, the hardware the physician needs to be able to access the information, and 24-hour monitoring to alert the doctor if anything appears to be wrong.

Because the device is portable, Knutson said it also is convenient for the patient to use at home or while traveling and that its operation doesn't depend on patient compliance. "This asks the patient to do nothing but go to bed at night," Knutson said. "The compliance is there."

According to Boston Scientific, the Latitude system will eventually be available for other types of heart failure devices too, such as pacemakers and

implantable cardioverter defibrillators. The company's medical devices are used in a broad range of interventional medical specialties.

Cardiacom launches diabetes telemonitoring

Cardiacom (Chanhasen, Minnesota) is adding blood glucose monitoring and the Autolink Diabetes Telemonitoring System to its existing telemonitoring devices for chronic diseases such as congestive heart failure, chronic obstructive pulmonary disease (COPD), asthma, coronary artery disease and obesity. The company also has formed a new division, GlucoCom, to focus on its diabetes products.

"We actually rolled out [the diabetes function] with some of our existing customers — two of our existing customers — in April of this year, but we have not formally launched it to the outside market customers until [now]," Jodie Root, vice president, sales and marketing for CardioCom, told *CDU*.

The new system consists of the GlucoCom Blood Glucose Monitor. The monitor collects glucose data and sends it to the secure GlucoCom Diabetes Management Web site using technology, specifically the AutoLink Blood Glucose Telemonitoring Device. The GlucoCom Blood Glucose Meter and Supplies, which Root described as a "high quality meter," can also be used as a standalone product.

Root said it is the "first time that we've taken one of our devices and linked it to a disease management web site that the patients themselves have access to." The web site gives patients secure login to access data about such things as the patterns of glycemic control or lack thereof.

To interact with care providers, patients can either print out the report for their care provider, email the report, or have a nurse or physician download it during an office visit, Root said. Perhaps even more important, the system also can be used for self-management of diabetes.

Health plans, disease management vendors and other disease management programs can use these tools, Root said. They can provide the device to their members toward the goal of better management of the disease. "The data can go to the nurse case manager who views it and calls the patient and works through a care plan for their physician, as necessary," said Root.

"What our customers told us was that the devices that we currently have . . . are great for the high-risk individual with multiple co-morbidities," Root said. "They are just too expensive for the broader diabetic population. We have people who have some high-risk disease, but largely a [diabetic] population that has a many-year chronic disease that needs to have glycemic control."

Home telemonitoring is positioned to become a broad necessity, Root said, because "America is an

aging population," with increasing rates of diabetes, heart failure, asthma, COPD and coronary artery disease. "The industry is now understanding" that using these types of devices makes sense, she said, for two reasons: "they are cost-effective because you can use fewer nurses, and you're more efficient, so you can interact with more patients."

WorldHeart to cut 50% of workforce

WorldHeart (Oakland, California), last month unveiled plans to restructure the company — reducing its workforce by half — to control spending and focus on developing its next-generation rotary ventricular assist device (VAD). In a teleconference reporting the restructuring, WorldHeart also disclosed that it expects to receive \$14.1 million from several existing investors, some new investors, as well as members of the company's management team.

"The financing and the significant restructuring plan are expected to fund our operations through the start of our U.S. clinical trials and on into [2Q08]," Jal Jassawalla, president/CEO of WorldHeart, said during the teleconference.

The restructuring will include a reduction in WorldHeart's workforce by 50-55 people, about 50% of its total employees, primarily at the Oakland, California and Heesch, the Netherlands, locations. WorldHeart expects to incur initial restructuring expenses of about \$700,000, primarily severance-related charges, in the 4Q06. Additional restructuring charges may be incurred and will be reported when available, the company said.

Richard Juellis, vice president, finance and CFO for WorldHeart, told teleconference listeners the company has seen a shift in demand away from first-generation VAD products to next-generation VAD products, which has resulted in a decline in sales of its first-generation Novacor LVAS.

Juellis said the company drew in \$1.4 million in 3Q06 revenues compared to \$2.2 million for 3Q05, and year to date revenue at nine months was \$7.7 million compared with \$8 million in 2005.

As a consequence, WorldHeart will reduce manufacturing, selling and administrative costs primarily associated with the Novacor LVAS, although the company plans to continue to support the product. These initiatives are designed to enable WorldHeart to focus its resources on preparing and qualifying the next-generation Levacor rotary VAD for clinical trials in the U.S., which are expected to begin in the second half of 2007, Jassawalla said.

Jassawalla said the restructuring will put the company in a favorable position to address the growing market for next-generation devices. He also said that he believes the trend in the industry toward next-generation technology is positive for the industry overall and for the company.

Hansen files IPO pricing

Hansen Medical (Mountain View, California) a company developing robotic technology for the accurate positioning, manipulation and stable control of catheters and catheter-based technologies, filed a prospectus with the Securities and Exchange Commission for a 6.25 million share initial public offering priced at between \$11 and \$13 a share. If priced at the midpoint, the deal would be valued at \$75 million before expenses.

The company first filed for its IPO back in August but at the time had not determined the actual number of shares and per-share price.

Hansen Medical says robots can help doctors take better care of their cardiac patients. The company's Sensei system, which includes an electromechanical robot, assists in guiding the movement of diagnostic catheters for hard-to-reach places in the heart.

Currently in trials for FDA approval, the Sensei system and Artisan control catheters are designed to help simplify cardiology procedures and decrease treatment time.

Founded in 2002, the company plans to use IPO funds for product development, research, sales and marketing, and administrative activities. Chairman Russell Hirsch owns about 23% of the company through Prospect Venture Partners and affiliates.

In its original filing in August, the company noted that it has experienced substantial net losses since its inception in late 2002. It reported net losses of about \$4 million in 2003, \$7.1 million in 2004, \$21.4 million in 2005 and \$11.4 million in the six months ended June 30, and as of June 30, the company had accumulated deficit during the development stage of \$44.4 million. The company noted that it anticipates continued losses "for the foreseeable future."

PAD brings \$25M for Pathway

Pathway Medical Technologies (Redmond, Washington), a developer of endovascular treatments for peripheral arterial disease (PAD), last month closed a \$25 million Series B round of financing, a little more than a year after closing a Series A round of \$15 million. According to Tom Clement, president/CEO of the company, Pathway initially had thought it would not seek another round of financing for at least another year, but an excellent opportunity presented itself.

"It was more money available at an excellent valuation," Clement told *CDU*. "It also gives us the money now to work right through a product launch and well into revenue streams."

Pathway manufactures the Pathway Atherectomy system for treating PAD, and Clement said that Pathway expects to launch the product in the U.S. some time in early 2008, once FDA approval is garnered.

In 2004, the now eight-year-old company was struggling in its development of a device to remove fatty deposits of plaque from arteries in the heart, and

had been forced to lay off employees. The company then decided to design the device to treat the arteries in the leg and started attracting capital, including the Series A round in March 2005.

Two new investors joined the financing round: lead investor HLM Venture Partners and Latterell Venture Partners. In addition, existing investors ABN AMRO Capital Lifesciences, Giza Ventures and Oxford Bioscience also participated.

EP MedSystems in two settlements

EP MedSystems (West Berlin, New Jersey) reported executing a settlement with the Bureau of Industry and Security of the U.S. Department of Commerce to close issues related to its shipment of products to restricted countries in 2004 and earlier. The company does not admit or deny guilt, but agreed to pay a fine of \$244,000 with no restrictions on commercial or export activities. The company said it has accrued \$345,000 for this penalty in its books as of June 30.

The company said also that it has made a settlement offer to the U.S. Department of the Treasury in connection with an investigation of these shipments and is awaiting a response. It said the Treasury Department has indicated to it “orally” that the maximum penalty it might seek would be \$44,000.

Given that investigations by the Treasury Department or the Securities and Exchange Commission have not been closed, the company said it could not rule out additional penalties. But it said it has made no provision for any future costs associated with these investigations.

EP MedSystems develops cardiac electrophysiology (EP) products used to diagnose and treat certain cardiac rhythm disorders.

VNUS reports ruling vs. rivals

VNUS Medical Technologies (San Jose, California) reported that a federal judge ruled in its favor on the meaning of several claims in a lawsuit against several rival companies. In October, VNUS filed patent infringement lawsuits against **AngioDynamics** (Queensbury, New York) and **Vascular Solutions** (Minneapolis). VNUS already had a standing suit against **Diomed Holdings** (Andover, Massachusetts). The suits pertain to devices that use lasers to burn away tissue inside veins. The lawsuit asks for an injunction and monetary damages.

The decision by the U.S. District Court for the Northern District of California determined the meaning of certain words and phrases in the lawsuit, VNUS said. The ruling was favorable to the company, according to VNUS.

Diomed had a different take on the ruling. “This claim construction ruling clears the way for Diomed to proceed with its defenses that the VNUS patents are not infringed by Diomed’s EVLT methodology

and, further, that the VNUS patents-in-suit are deficient and should be struck down,” said David Swank, CFO of Diomed Holdings.

Bioheart to expand MyoCell trials

Bioheart (Sunrise, Florida), a developer of cell therapies for damaged heart muscle, reported expansion of its U.S. and European trials of its MyoCell adult myogenic (muscle) stem cell composition and MyoCath needle-injection catheter product candidates.

MyoCell, a clinical therapy for treating damage to the heart in patients in Class II or Class III heart failure, uses myoblasts — precursors to muscle cells, derived from a patient’s own thigh muscle — to produce implants placed into the heart via catheter. When injected into scar tissue within the heart, myoblasts can develop into contractile muscle cells and integrate with heart muscle and/or release potentially beneficial proteins.

MyoCath, a catheter delivery system, delivers cell therapy or other compounds directly into the heart muscle via needle injection.

“After more than 19 years of development and testing, large scale clinical studies are being expanded by statistically significant numbers with an additional 450 plus patients,” said Michael Brown, MD, PhD, senior clinical scientist at Bioheart.


Bioheart completed enrollment in the U.S. in the fourth and final cohort of its dose-escalation, Phase I clinical trial, known as the MYOHEART trial. In this final cohort, patients received a high-dose injection of 675 million cells, compared to 25 million, 75 million and 225 million cell doses in previous cohorts.

Bioheart then finalized the protocol for its U.S. Phase II randomized double-blind, placebo-controlled MYOHEART II clinical study and has submitted this protocol to FDA for review. This study has been designed to enroll up to 450 patients at roughly 40 centers to confirm the safety and efficacy of adult myogenic stem cell transplantation for heart failure.

W.L. Gore launches AAA resource

W. L. Gore & Associates (Gore; Flagstaff, Arizona) reported the launch of a new patient education resource to help provide information about the causes, symptoms and available treatments for abdominal aortic aneurysms (AAA).

The resource, part of broader content and feature improvements to www.goremedical.com, guides visitors through a “television-like” experience that addresses questions and concerns commonly raised by those affected by AAA. Each year about 200,000 people in the U.S. are diagnosed with AAA.

The company said the Gore AAA Patient Information Resource is designed to educate the public about the condition and its treatment options, which include medication, open surgical repair and endovascular surgery. — 

Agreements

- **Cardiac Science** (Bothell, Washington) has signed an amendment to its agreement with **GE Healthcare** (Little Chalfont, UK) which extends the agreement's term to five years from the original three years. GE Healthcare, a division of **General Electric**, will sell Cardiac Science's "crash cart" defibrillator/monitor to hospitals in the U.S. and Canada under Cardiac Science's Powerheart brand, and to customers outside North America under the GE Responder brand. GE and Cardiac Science said they have partnered to refine the product specifications and features to ensure successful launch. Arrangements were also made to support GE's worldwide service model. Product shipments are being made under a pilot program. The defibrillator/monitor is a rugged portable device with resuscitation and pacing therapies for use by professionals. The pilot program tests worldwide launch by shipping finished devices to customers as well as service kits to GE service centers. Full shipments will begin upon the completion of the pilot program.

- **Wyndgate Technologies** (Denver) reported that **Hospital Partners of America** (HPA; Charlotte, North Carolina) is implementing Wyndgate's SafeTrace Tx transfusion management system at **St. Joseph's Medical Center** (Houston), the second HPA facility to implement the system. HPA first licensed the SafeTrace Tx system for its **Twelve Oaks Medical Center** (Houston). When St. Joseph's learned that it would need to purchase a new blood bank system because its existing system was being discontinued, HPA licensed SafeTrace Tx based on the success of the system at Twelve Oaks, Wyndgate said.

- **Clinical Data** (CLDA; Newton, Massachusetts) and **Quintiles Transnational** (Research Triangle Park, North Carolina) reported an alliance to offer Quintiles' customers CLDA's services related to the evaluation of drug-induced QT prolongation. The QT interval is a part of the normal heartbeat which can be prolonged as a side effect of some drugs. People with prolonged QT intervals are susceptible to abnormal heart rhythms, Janine McCargo, a spokeswoman for Clinical Data, told *Cardiovascular Device Update*. The pharmacogenomics analyses are performed in the laboratories of Clinical Data's service division, **Cogenics** (New Haven, Connecticut). As part of the alliance, the two companies may also collaborate on the study of drug-induced QT prolongation for potential development of new products or services. Quintiles provides services for drug development, information, financial partnering and commercialization for the pharmaceutical and biotech industries. CLDA provides molecular and pharmacogenomics

services as well as genetic tests and is organized into three worldwide divisions: PGxHealth, Cogenics and Vital Diagnostics. Terms of the agreement were not disclosed.

- **Cerner** (Kansas City, Missouri) and **Mortara Instrument** (Milwaukee), a non-invasive cardiology technology company, said they will pursue a joint engineering effort utilizing DICOM to provide full diagnostic capabilities within an electronic medical record (EMR). The companies said that the use of the DICOM ECG standard allows the EMR to receive and present raw ECG data seconds after it has been acquired. Combining the diagnostic ECG with the EMR now opens the door for more advances in ECG, as greater EMR data can be properly utilized, they said. The agreement enables Cerner to provide the E-Scribe ECG functionality within the Millennium platform as part of PowerChart ECG to improve ECG workflow in other Cerner solutions, including PowerChart EMR, iNet for the ICU, FirstNet for the emergency room and CVNet for cardiology. The DICOM standard allows for movement, reporting and viewing of data from this ubiquitous diagnostic regardless of which ECG manufacturer's equipment is used to acquire the data. Mortara develops non-invasive cardiology for innovations that are core to the company's line of ECG products, including electrocardiographs, stress exercise systems, Holter systems, data warehousing, and cardiology monitoring systems.

- The **Medical University of South Carolina** (MUSC; Charleston, South Carolina) and **Siemens Medical Solutions** (Concord, California) have entered into a five-year, \$40-million strategic alliance that will bring leading diagnostic technologies to MUSC's departments of cardiology and radiology. The agreement will include introducing the latest technology in MUSC's **Heart & Vascular Center**, which brings together advanced cardiology and interventional radiology services in the same facility. MUSC will have access to Siemens systems for angiography, digital radiography, CT, MRI and PET. MUSC and Siemens also will collaborate on R&D activities. Siemens will also work to improve workflow to advance MUSC's emphasis on advance patient care. An example of Siemens technology being utilized at MUSC is the recently installed Somatom Definition dual-source CT system, which incorporates two X-ray sources and two detectors in a single scanner. Through this alliance, imaging equipment will share the Siemens syngo operating platform, which has a standard user interface and enables operational and workflow improvements such as faster training of physicians and staff.

Market and Technology

Cleveland Clinic in new treatment for atrial fibrillation

Pulmonary vein antrum isolation (PVAI), a new treatment for atrial fibrillation (AF), has been found to produce regression in irregular heartbeats in most patients and improves heart failure patients' quality of life, according to a new study by the **Cleveland Clinic** (Cleveland), presented at this year's Scientific Sessions of the **American Heart Association** (AHA; Dallas). The clinic said that the lengthily named trial, Pulmonary Vein Antrum Isolation vs. AV Node Ablation with Bi-Ventricular Pacing for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure (PABA CHF), is the first randomized, controlled study to compare two current approaches to treating AF in patients with congestive heart failure.

PVAI is used to electrically isolate all four pulmonary veins from the left atrium. During the procedure, also known as pulmonary vein ablation (PVAI), catheters are inserted into the blood vessels of the atrium, and frequency energy is then used to block the pathway of irregular heartbeats.

During AV node ablation with biventricular pacing (AVNA/BiV), a catheter is used to deliver an electrical current to the part of the heart causing the AF to prevent the irregular heartbeats. The patient relies on the use of an implantable cardioverter defibrillator (ICD) to shock the heart into normal rhythm when AF arises.

"The study results suggest that PVAI is superior to AVNA/BiV in terms of both freedom from atrial fibrillation and improving patients' quality of life," said Andrea Natale, MD, section head of electrophysiology and pacing at Cleveland Clinic. "Given many patients are afflicted by both congestive heart failure and atrial fibrillation, PVAI is a real treatment option."

Recent studies have shown that patients who are pacemaker-dependent may benefit more from a biventricular device than a standard dual chamber device. "The question then becomes, is it better to cure the atrial fibrillation with pulmonary vein ablation or make patients pacemaker-dependent," Natale said. "More research needs to be done to answer this very important question."

Medicaid cardiac care faulted

The quality of cardiac care for Medicaid patients lags behind the care given to those with HMOs and

private insurance according to a new study. The study by Dr. James Calvin, lead study author and director of cardiology at **Rush University Medical Center**, (Chicago), found Medicaid patients were less likely to receive short term medications and to undergo invasive cardiac procedures. They also had higher in-hospital mortality rates and were less likely to receive recommended discharge care. Differences were fewer and smaller for Medicare patients. The study was published in the Nov. 21 issue of the *Annals of Internal Medicine*.

In addition to Rush, study participants included **Duke University Medical Center**, **New York University School of Medicine**, **Northwestern University School of Medicine**, **University of Cincinnati College of Medicine**, and the **University of North Carolina at Chapel Hill**.

The researchers evaluated data from more than 37,000 patients younger than 65 and more than 59,000 patients 65 and older at 521 U.S. hospitals. All patients had acute coronary syndromes. These symptoms occur when there is insufficient blood supply to heart muscle. If the blockage lasts long enough, the muscle dies causing a heart attack.

The study measured the use of the recommended guidelines of the **American College of Cardiology** and the **American Heart Association**. Those guidelines include recommended medications within the first 24 hours, medications and dietary advice to control cholesterol levels, counseling to stop smoking, and cardiac rehabilitation programs.

When compared to patients with HMO or private insurance, Medicaid patients were less likely to receive aspirin, beta-blockers, clopidogrel, and lipid-lowering agents. Medicaid patients were also less likely to receive dietary counseling, smoking cessation counseling, and referral for cardiac rehabilitation. Gaps also existed for acute care. Delays were observed for Medicaid patients in the time to first electrocardiogram and in time to cardiac catheterization and revascularization when these procedures were performed.

Medicaid patients had higher in-hospital mortality rates (2.9% vs. 1.2%) and after adjustment, the risk for death was approximately 30% higher in Medicaid patients compared to those with HMOs and private insurances. Mortality rates were not significantly different for Medicare patients.

The patients evaluated in the study were from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early implementation of the ACC/AHA guidelines) quality improvement initiative. Data was collected from January 2001 through March 2005.

Causes of diastolic heart failure probed

A new study shows that blood flow to the legs

is relatively normal in people with diastolic heart failure, suggesting other potential causes of their inability to do everyday activities, according to researchers at **Wake Forest University Baptist Medical Center**.

“Reduced tolerance for physical activity is the primary symptom of diastolic heart failure, and it greatly affects quality of life,” said Dalane Kitzman, MD, professor of cardiology and senior researcher on the study. “This condition will increase as our population ages, so it’s important to pinpoint the reasons for their symptoms and to develop effective treatments.”

The study results are reported on-line in *American Journal of Physiology — Heart Circulation Physiology* and will be published in an upcoming print issue.

Cardiac IVD to exceed \$45B billion by 2010

The *Cardiac Markers* report from **Kalorama Information** (New York) predicts that the world market for cardiac IVDs will grow to more than \$4.5 billion by 2010, on the heels of advances in testing such as recently discovered genetic factors. Kalorama said that tests such as inflammation and homocysteine markers — relatively rare only a few years ago — are now part of the standard cardiac marker segment.

Overall growth in IVD cardiac marker tests will derive from new markers, such as ultra-sensitive CRP, plasminogen activator inhibitors, s100 protein, p-selectin, soluble fibrin, glycogen phosphorylase-BB, and thrombus precursor protein, among others, according to the report.

The impact of these emerging markers and tests will be most notably seen in Western markets, with the U.S. currently accounting for 45% of the market, Europe 27%, and Japan 13%. Cost, availability and technological resources still make such tests relatively prohibitive in the rest of the world, the report said.

The study examines tests and technologies currently available and those expected to take their place in the near future.

Kalorama is a division of MarketResearch.com which supplies independent market research for the life sciences.

Transplant centers warned by CMS

The **Centers for Medicare and Medicaid Services** (CMS) in late November sent letters notifying two heart transplant centers that the agency will withhold Medicare funding from their programs for not meeting the minimum federal standard of performing 12 transplants per year, the *Los Angeles Times* reported.

In June, the Times reported that an investigation found 20% of the 236 federally funded heart, liver and lung transplant programs do not meet minimum CMS standards for the number of procedures performed

and survival rates. Nine lung transplant programs and 36 heart transplant programs did not meet CMS standards, and those programs accounted for 71 more deaths within one year than expected under normal conditions, based on a government analysis of survival rates.

CMS has the authority to revoke the certification of transplant programs that fail to meet agency standards. In August, CMS began to issue warning letters to about 35 transplant programs that have failed to meet agency standards and requested that the centers make improvements before action was taken.

CMS notified the heart transplant programs at Wake Forest University Baptist Medical Center, which performed two transplants in 2005, and **Montefiore Medical Center** (New York), which performed no transplants, that they will no longer receive Medicare funding.

A third program at **St. Louis University Hospital**, which also performed no transplants last year, voluntarily relinquished its Medicare funding after receiving a warning.

CMS Chief Medical Officer Barry Straube said, “It might be possible that people were not taking this seriously enough and thinking that we would not take this action.”

The centers have 30 days to challenge the withdrawals.

Study: SBP rises sooner in boys

A Canadian study suggests that the reason men tend to have higher systolic blood pressure (SBP) than women could be because as boys get older their SBP tends to be higher than girls of equivalent age. The results of the five-year study, titled “Emergence of Sex Differences in Prevalence of High Systolic Blood Pressure: Analysis of a Longitudinal Adolescent Cohort,” appeared in the December issue of *Circulation*, a journal of the AHA.

The researchers tracked a group of 1,200 adolescents from 1999 to 2005 and took measurements at grades 7, 9 and 11. They found the incidence of high SBP at grade 7 to be split about 50-50 between boys and girls. However, as the group reached grade 11 the high SBP group comprised 67% boys.

The study also suggests that for both male and female adolescents, reducing sedentary behavior and increasing physical activity may lower SBP, even if they are overweight. ————— 🌐

Next month in CDU —

*Complete coverage of the FDA’s
two-day public meeting on
drug-eluting stents.*

Personnel File

- Robert Mitchell has been hired as executive VP and chief operating officer of **AngioDynamics**. (Queensbury, New York), a new position. Previously, Mitchell was president/CEO and director for Millimed Holdings. AngioDynamics provides medical devices for the minimally invasive diagnosis and treatment of peripheral vascular disease.

- Jeffrey Langan has been named president/CEO of **Cambridge Heart** (Bedford, Massachusetts). Langan succeeds David Chazanovitz, who resigned after six years as president/CEO. Langan has served as a member of the company's board since 1999. Langan is founder and a principal of Maine Point Associates, a business consulting firm. He also served on the business advisory board of Ophtherio. Cambridge Heart develops products for the noninvasive diagnosis of cardiac disease.

- Steven Van Tyle has been promoted from director of international sales to vice president of global sales at **HydroCision** (Billerica, Massachusetts). Prior to joining HydroCision, Van Tyle served as vice president of sales for Raymedica. He also has served in senior executive sales-and-marketing positions at Cryolife, Organogenesis, the SSI division of Hillenbrand Industries, and at Ayerst Laboratories, a division of American Home Products. HydroCision develops fluidjet-based surgical tools.

- Mark Carlson, MD, has been named chief medical officer and senior VP, clinical affairs, of the cardiac rhythm management division of **St. Jude Medical** (St. Paul, Minnesota). And Peter Spadaro has been promoted to the newly created position of U.S. division VP for vascular sales. Carlson most recently served as professor of government relations at Case Western Reserve University. Spadaro — who has worked in the med-tech industry for almost 25 years and has been with St. Jude for nearly 20 years — will have overall U.S. sales responsibility in the areas of cardiology, cardiac surgery and surgical atrial fibrillation (AF). St. Jude has five major focus areas that include: cardiac rhythm management, AF, cardiac surgery, cardiology and neuromodulation.

Product Pipeline

CVRx wins IDE for pacemaker-like hypertension device

If ongoing trials are successful, the device sector may one day have another innovative implantable technology, this one used to treat difficult-to-manage high blood pressure, particularly in patients who have a resistance to hypertension drugs. **CVRx** (Minneapolis) reported that it has received FDA approval for a conditional investigational device exemption (IDE) to begin a pivotal clinical to evaluate the safety and effectiveness of its Rheos baroreflex hypertension therapy system, an implantable device to treat high blood pressure.

The blinded study, sponsored by the company, is a prospective, randomized, multi-center trial that will be conducted at up to 40 sites in the U.S. The study seeks to determine the safety and effectiveness of the Rheos System when used in drug-resistant hypertension patients. To be enrolled in the trial, patients need to be resistant to treatment with at least three anti-hypertension agents, including a diuretic. Their systolic blood pressure must be greater than or equal to 160 mmHg. Data from this clinical trial is intended to support the pre-market approval application for the Rheos system to the FDA.

The Rheos system, CVRx's flagship product, is intended for use in patients who cannot control their blood pressure with medications, or medication combined with lifestyle modifications. The device provides what physicians might describe as a "physiologically rational" method to reduce blood pressure. It is designed to do this with the use of mild electrical signals to influence the body's blood pressure regulation system, called the baroreflex.

According to Robert Kieval, founder and current vice president and chief technology officer of CVRx, the Rheos is a pacemaker-like device designed to stimulate tissues within the body. "We stimulate areas of the vascular system that have sensors in them that report blood pressure to the brain," he told *Cardiovascular Device Update*. "The brain compares what it believes is the blood pressure to the needs of the body and then makes the appropriate adjustments."

Kieval said that the signals that the device generates are interpreted by the body as a rise in blood pressure that needs to be corrected. The brain then works through the body's own blood pressure control mechanisms to attempt to restore blood pressure to

normal. Thus, in essence, it fools the body and leads to a net reduction in blood pressure. Kieval likened this mechanism of action to the ability to cool a room by holding a match under a thermostat: "The heat of a match fools the thermostat into thinking that the entire room has become too warm and causes the air conditioning system to be activated."

The device has thus far enjoyed early clinical success in European and U.S. feasibility clinical trials for its evaluation. European patients started enrolling in the trial in 2004. Early results for the first 12 patients were reported at the European Society of Hypertension meeting in June 2006.

Elsewhere in the product pipeline:

- **Boston Scientific** (Natick, Massachusetts) reported the launch of software enabling its Left Ventricular (LV) Offset feature in the company's Contak Renewal, Renewal 3, and Renewal 3 RF cardiac resynchronization therapy defibrillators (CRT-D). LV Offset allows physicians to further fine tune synchronization of the heart by allowing adjustment of the delay between right and left ventricular pacing, which helps physicians provide more tailored care for heart failure patients. The software will operate on the Zoom Latitude programmer and allow patients who have already been implanted with a Contak, Renewal 3 or Renewal 3 RF CRT-D to have the LV Offset feature activated. The LV Offset feature can be enabled by the Zoom Latitude programmer during a patient's routine in-clinic visit. Boston Scientific CRM said it will begin providing the FDA-approved software to physicians "in the coming weeks."

- **Cardica** (Redwood City, California) received FDA 510(k) clearance to market its C-Port xA Distal Anastomosis System. The system automates the creation of anastomoses, or attachments of blood vessels and grafts, such as those in coronary artery bypass graft (CABG) surgeries. The system is designed to deploy staples around the periphery of the anastomosis to help provide leak-proof sealing. Other features include improved access to the coronary artery and reduction of target site preparation; optimization of the staple configuration; and incorporation of vessel clamps for ease of loading the graft vessel for anastomosis. The C-Port xA system received the CE mark in July 2006 and is currently marketed in Europe. Cardica designs and manufactures automated anastomosis systems for CABG surgery.

- **CardioDynamics** (San Diego), a developer of BioZ impedance cardiography (ICG) technology, reported the publication of a cost-effectiveness study in the Fall 2006 edition of *American Heart Hospital Journal*. The study showed that use of ICG was cost-effective in both the short and long term compared to standard care treatment of uncontrolled hypertension. In the previously-published CONTROL trial, use of ICG in the treatment of uncontrolled hypertension result-

ed in an 8 mm Mercury (mm Hg) greater systolic blood pressure (BP) reduction and a 7 mm Hg greater diastolic BP reduction than standard care. Until the completion of this study, it was unknown whether the clinical benefits of using ICG in uncontrolled hypertension could also be considered cost-effective, CardioDynamics said. The short-term cost-effectiveness analysis demonstrated that the additional BP reduction with ICG care in the CONTROL trial was achieved at a significantly lower incremental cost than the cost of reducing blood pressure with standard care. ICG care incremental cost per mm Hg reduced was \$20 for systolic blood pressure (44% less than standard care's \$36 cost per mm Hg reduced) and \$23 for diastolic blood pressure (71% less than standard care's \$79 cost per mm Hg reduced).

- **CardioVascular Technologies** (Palo Alto, California) has received a Notice of Allowance for its patent application, titled "Vascular Couplers, Techniques, Methods, and Accessories." The coupler system enables clampless coronary artery bypass graft (CABG) surgery, minimizing aortic manipulation and embolic dislodgement by not requiring cross-clamping or aortic side-biting during the procedure. By not utilizing a clamp on the aorta, the system is designed to reduce the incidence of postoperative cognitive dysfunction, which occurs in up to about 50% of patients undergoing CABG procedures. The sutureless vascular coupler system can be used during cardiopulmonary supported procedures, as well as off-pump/beating heart, minimally invasive direct coronary artery bypass (MIDCAB), endoscopic or robotically assisted surgical procedures. CardioVascular Technologies specializes in developing surgical and catheter-based technologies.

- **CoreValve** (Irvine, California) said that its ReValving System, consisting of an 18 Fr size delivery catheter, was used to percutaneously implant its porcine pericardial-tissue bioprosthesis over the severely calcified aortic heart valve of an 89-year-old female patient. In contrast to long post-surgical recuperation times, this "pure" PAVR patient was discharged from the ICU to the general ward on the morning after her ReValving procedure and was fully mobile and awaiting discharge from the hospital, the company said.

- **CryoCath** (Montreal) has received notification from the FDA allowing the company to expand its pivotal investigational device (IDE) STOP AF trial. The company can now enroll up to 150 patients in up to 20 centers. To date, five centers have received Internal Review Board (IRB) approval and have begun screening patients, including 16 that have already been enrolled and randomized. As many as 250 patients, randomized into two arms, will be enrolled to complete the trial. One cohort will receive cryoablation therapy with Arctic Front (the ablation arm);

the other will receive currently prescribed drug therapies (the control arm). For every two patients in the ablation arm, there will be one in the control arm. Patients in the trial will be highly symptomatic paroxysmal atrial fibrillation (AF) patients who have failed at least one anti-arrhythmic drug. The trial's primary endpoint will be the absence of detectable AF at the end of the 12-month follow-up period. The trial's design also allows patients randomized into the drug arm to cross over into the ablation arm if they do not show improvement. Arctic Front is a minimally invasive cryo-balloon catheter designed specifically to treat AF. This bi-directional, double balloon catheter enables physicians to rapidly isolate all four pulmonary veins for the treatment of AF. Approved in Europe, it has treated more than 300 patients in more than 18 centers. CryoCath makes cryotherapy products to treat cardiovascular disease.

- **CryoCor** (San Diego) has filed a pre-market approval (PMA) application for the treatment of atrial flutter (AFL). CryoCor said it has developed a disposable catheter system based on its proprietary cryoablation technology for the minimally invasive treatment of cardiac arrhythmias. The Cryoablation System is designed to treat cardiac arrhythmias through the use of cryoenergy, or extreme cold, to destroy targeted cardiac tissue. In the U.S., CryoCor is conducting a pivotal trial to evaluate the safety and efficacy of the Cryoablation System for the treatment of AF, and has submitted a PMA for the treatment of AFL. CryoCor is a medical device company focused on the treatment of cardiac arrhythmias.

- **diaDexus** (South San Francisco, California) reported the publication of a study showing that lipoprotein-associated phospholipase A2 (Lp-PLA2), a cardiovascular-specific inflammatory enzyme associated with unstable plaque, is a strong predictor of recurrent stroke. The report, based on the Northern Manhattan Stroke Study, appears in the Oct. 23 issue of *Archives of Internal Medicine*. The study followed 467 patients, diagnosed as having a first stroke, for about four years. Results showed that those with the highest levels of Lp-PLA2 had an increased risk of recurrent stroke, heart attack or vascular death, even after adjusting for factors such as age, sex, ethnicity and history of heart disease. Lp-PLA2 was measured using the diaDexus' PLAC test.

- **Diagnosoft** (Lutherville, Maryland) said it received FDA clearance for its Diagnosoft HARP software designed to assist in the analysis of MRI by providing quantitative measurements and visualization of regional heart function. Beta versions of the software have already been licensed for research purposes to more than two dozen research-oriented institutions around the world, the company said. With FDA approval, the software is now cleared for clinical applications and can be used by radiologists, cardiologists,

and pharmaceutical companies in assisting the diagnosis, staging, and monitoring heart disease as well as in the development of new therapies. Diagnosoft is a medical imaging company specializing in computer-aided diagnostic software.

- **FlowCardia** (Sunnyvale, California) reported that Naveen Sachdev, MD, from Providence St. Vincent's Hospital (Portland, Oregon) enrolled the first patient into the Peripheral Approach to Recanalization in Occluded Totals (PATRIOT) study. FlowCardia's 10-hospital, 85-patient PATRIOT U.S. pivotal study is designed to determine the safety and efficacy of the Crosser 14 and Crosser 18 Catheters for CTO recanalization in the upper and lower legs. The Crosser system is a monorail catheter delivered over standard .014" and .018" guidewires to the site of a CTO. The CROSSER uses high-frequency vibration to cross CTOs allowing for subsequent plaque debulking, balloon angioplasty and stent placement. For many patients with chronic occlusions in the legs, this minimally invasive, endovascular approach to CTO recanalization will eliminate the need for potentially traumatic bypass surgery or amputation, the company said. FlowCardia also announced FDA 501(k) submission for the CROSSER 14 coronary platform. The data used to support the coronary submission came from FlowCardia's 19-hospital, 125-patient U.S. FlowCardia's Approach to Chronic Total Occlusion Recanalization (FACTOR) pivotal study. FACTOR was designed to assess the safety and efficacy of the Crosser catheter for chronically occluded coronary artery recanalization.

- **Hydromer** (Branchburg, New Jersey) has developed an anti-thrombogenic polymer coating complex (F202) designed to minimize blood coagulation. The surface bonding capabilities of the F202 polymer, which maintains long-term non-leaching properties, "are outstanding on a wide variety of medical materials such as cardiovascular devices and stents, hemodialysis equipment and intravenous catheters," the company said. Hydromer said it will target device manufacturers who will enter into confidentiality agreements with non-analysis restrictions, submit their device samples for trial coating and provide feedback to Hydromer.

- **Instrumentation Laboratory** (IL; Lexington, Massachusetts) reported receiving FDA 510(k) clearance for its HemosIL Homocysteine assay, an automated, latex-enhanced immunoassay for the quantitative determination of total L-homocysteine (Hcy) in human citrated plasma on IL Coagulation Systems. Elevated levels of Hcy are associated with a variety of pathologies, particularly those which increase risk of cardiovascular disease and venous thromboembolism. HemosIL Homocysteine is the first fully automated Hcy assay dedicated to the Hemostasis laboratory, the company said. It allows for an extended thrombophil-

ia work-up on a single coagulation instrument, in combination with other specialty assays. Hcy is derived from the metabolism of methionine, an essential amino acid in the diet. The normal adult range of total Hcy is 5 - 15 $\mu\text{mol/L}$. An increase of 5 $\mu\text{mol/L}$ total Hcy corresponds to a 27% higher risk of venous thromboembolism (VTE). Instrumentation Laboratory makes in vitro diagnostic instruments, related reagents and controls for use primarily in hospitals and independent clinical laboratories.

- **MedicalCV** (Minneapolis) reported that it has been notified by the U.S. Patent Office that it will allow four of the company's patent applications covering various methods and apparatus for treating tissue, including treatments for atrial fibrillation. The coverage provides protection for use of both the company's minimally invasive system and the surgical wand products. MedicalCV develops products used by cardiac surgeons to ablate cardiac tissue to treat atrial fibrillation. Its core technology is the AtriLaze Ablation System.

- **Orgis Medical** (Lake Forest, California) reported that the U.S. Patent and Trademark Office has granted the company its 13th patent, "Implantable Heart Assist System and Method of Applying the Same." The patent covers the miniaturization of the company's Cancion and Exeleras systems for direct placement of a pump, blood flow conduits and pump control electronics directly into the vasculature of congestive heart failure patients. The Cancion system is being studied in the MOMENTUM pivotal trial and the first clinical use of the Exeleras system is expected next year.

- **PLC Systems** (Franklin, Massachusetts) said the FDA has granted conditional approval of an investigational device exemption to conduct a pilot clinical trial to evaluate the safety of the RenalGuard system and to measure and balance fluid inputs and outputs in patients undergoing a catheterization procedure where contrast media will be administered. RenalGuard is designed to provide balanced replacement hydration therapy to high-risk patients undergoing imaging procedures where contrast agents are administered. PLC develops technologies for the cardiac and vascular markets.

- **Possis Medical** (Minneapolis) reported receiving FDA clearance for its AngioJet Xpedior catheter to remove thrombus from peripheral veins. The Xpedior, used with Possis' AngioJet System, is the only device cleared for removing thrombus — a treatment known as thrombectomy — in peripheral veins, according to Possis. The Xpedior catheter is cleared for removing thrombus from upper- and lower-extremity peripheral veins 3 mm and larger in diameter and it is cleared for vascular use with Possis' Power Pulse Delivery, a procedure that sprays smaller doses of clot-dissolving medicine directly

into the thrombus and then quickly removes the softened clot material. Possis said the AngioJet System used for venous thrombectomy is identified as a reimbursable procedure for both physicians and hospitals. The company estimates that the realizable market opportunity for venous thrombectomy now exceeds \$85 million, and will grow to more than \$100 million by 2010.

- **Radiant Medical** (Redwood City, California) reported initiation of its COOL RCN trial, a safety and efficacy study of catheter-based cooling in patients undergoing cardiac catheterization at risk of developing radiocontrast nephropathy. The Reprieve Endovascular Temperature Therapy System is designed to enable the rapid induction of hypothermia in a conscious or unconscious patient by use of a venous heat exchange catheter. A catheter is threaded into the femoral vein and positioned in the inferior vena cava. As cool sterile saline is circulated within the catheter, blood flowing past the catheter is cooled, and the blood then reduces the body temperature. To rewarm the patient, the sterile saline within the catheter is simply warmed. Radiant's endovascular temperature therapy systems are to treat patients with acute ischemic or inflammatory medical conditions, such as heart attack, radiocontrast nephropathy, stroke and cardiac arrest.

- **Siemens Medical Solutions** (Malvern, Pennsylvania) is introducing the Axiom Artis dBA Twin, an imaging system designed for universal angiography and the highly specialized field of neuroradiology, at this week's scientific assembly and annual meeting of the **Radiological Society of North America**. The Axiom Artis dBA Twin is a milestone in advanced biplane imaging. The system features the largest biplane anatomical coverage available, and is uniquely equipped with two 30 x 40-cm flat detectors. The Axiom Artis dBA Twin provides flexibility across a complete applications spectrum, from neuroradiology to cardiac imaging, with fine detail resolution in 2-D and 3-D. Flat detector biplane technology delivers exceptional detail resolution to support both diagnostic and interventional decision making, the company said. The system supports the latest cross-sectioning 3-D imaging techniques with the optional syngo DynaCT cross-sectional imaging capability.

- **Spectranetics** (Colorado Springs, Colorado) reported that it has received FDA clearance to market its Turbo elite product line for the treatment of blockages within leg arteries. The Turbo product line is designed for improved pushability, trackability, and ablation capability as a result of an improved outer jacket and inner guidewire lumen, and additional laser fibers in most sizes, the company said. Spectranetics makes single-use medical devices used in minimally invasive surgical procedures within the car-

diovascular system in conjunction with its excimer laser system.


- **Stereotaxis** (St. Louis) reported FDA 510(k) clearance of its Niobe magnetic navigation system for use in neurovascular and peripheral applications with the company's family of Cronus magnetically enabled .014" vascular guidewires. Stereotaxis had previously received FDA clearance to use the Niobe System and Cronus guidewire family in coronary vasculature procedures only. The Cronus guidewire family will now integrate with the Niobe magnetic navigation system to provide precise magnetic guidewire navigation in coronary, neurovascular and peripheral anatomy. "[T]his clearance provides us with the flexibility to do so at a time of our choosing," said Bevil Hogg, president/CEO of Stereotaxis. Stereotaxis' instrument control systems are used in the interventional surgical suite.

- **St. Jude Medical** (St. Paul, Minnesota) reported FDA approval of its new tachycardia software for the Merlin Patient Care System, a computer used to program and interrogate cardiac rhythm management devices like pacemakers and implantable cardioverter defibrillators (ICDs). The software upgrade, which will be launched over the coming weeks, extends the benefits of the previously released Merlin graphical user interface to both St. Jude Medical pacemaker and ICD products. The Merlin Patient Care System, which received FDA approval in April 2006, is a programmer designed to help physicians conduct tests and analyze therapeutic and diagnostic data more efficiently.

- **Tryton Medical** (Newton, Massachusetts) reported completion of the company's first 10 clinical cases using its Side-Branch Stent and that all patients in the trial had coronary blockages involv-

ing a side branch and were successfully treated using the stent without any in-hospital complications. Richard Davis, co-founder and chief technical officer of Tryton said these bifurcated lesions account for 20% of all coronary lesions treated. He said the new Side-Branch Stent functions like a standard workhorse stent, but its specific task is to treat bifurcated lesions. The typical way to treat bifurcated lesions is to "provisionally" span the Y with a straight stent, in the hope of saving one vessel and, if there is enough blood flow afterwards, attempting to save the second vessel. The company says that the Side-Branch Stent is designed to save the side branch, and at the same time providing blood flow and access to the main vessel.

- **Vascular Solutions** (Minneapolis) has received FDA 501(k) clearance for its D-Stat Dry hemostatic bandage. The company said the product reduces time to hemostasis in patients undergoing diagnostic femoral catheterization procedures. The D-Stat Dry hemostatic bandage is a thrombin-based pad together with an adhesive bandage that can be applied for rapid control of topical bleeding. Vascular Solutions develops solutions for interventional radiology and cardiology.

- **Viasys Healthcare** (Conshohocken, Pennsylvania) reported receiving FDA 510(k) clearance for its Sonara and Sonara/tek digital Transcranial Doppler (TCD) systems and introduced that it the systems at the Medica meeting in Düsseldorf, Germany. TCD is a noninvasive method of measuring blood flow velocities in the arteries of the brain using ultrasound Doppler technology. Sonara and Sonara/tek systems were developed with a new digital data acquisition approach which is designed to provide higher resolution data. 

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