

## Cardiovascular Device Update

### Conference Data Focus on Transcatheter Valves and Ventricular Assist Devices

#### Companies

**Abbott** (ABT)  
**Abiomed** (ABMD)  
**Boston Scientific** (BSX)  
**Direct Flow Medical** (private)  
**Edwards Lifesciences** (EW)  
**HeartWare** (HTWR)  
**Johnson & Johnson** (JNJ)  
**Medtronic** (MDT)  
**St. Jude Medical** (STJ)  
**Thoratec** (THOR)

#### Products

**Bioabsorbable scaffold** (ABT)  
**Impella** (ABMD)  
**Direct Flow Valve** (Direct Flow)  
**Sapien Transcatheter Heart Valve** (EW)  
**Entrada** (transapical valve MDT)  
**Xience** (everolimus DES by ABT)  
**Cypher** (sirolimus DES by JNJ)  
**Nevo** (sirolimus DES by JNJ)  
**Taxus** (paclitaxel DES by BSX)  
**Promus** (everolimus DES by BSX)  
**Endeavor** (zotarolimus DES by MDT)  
**Resolute** (zotarolimus DES by MDT)  
**HeartMate LVAD** (THOR)

#### Heart Valves:

- Physician response to the PARTNER Cohort A data comparing Transcatheter Aortic Valve Implantation (TAVI) to surgery is overwhelmingly positive, despite the trial's mixed results, a trend that could benefit **Edwards Lifesciences (EW)**, **Medtronic (MDT)**, and **DirectFlow** (privately held).
- *inThought* expects the FDA will approve Edwards' Sapien device by early 2012 for surgery-ineligible patients. Medtronic's CoreValve now has 35 sites studying its TAVI. DirectFlow continues study of its re-positional TAVI.

#### Ventricular Assist Devices:

- The May 10<sup>th</sup> edition of the *Journal of the American College of Cardiology* reported outcomes from a bridge-to-transplant post approval study on **Thoratec's (THOR) HeartMate II**, showing 6-month survival at 90% and 1-year at 85%, an improvement over other left ventricular assist devices (LVADs).
- **HeartWare (HTWR)** reported data at the International Society of Heart and Lung Transplantation (ISHLT) meeting showing **94% survival** in 250 patients at 6-months, but clot risk was higher than expected.
- Data on **Abiomed's (ABMD) Impella** device has been well received. The medical community continues to adopt this unloading device in the place of intra-aortic balloon pumps.

## Heart Valve Update

Aortic valves may be replaced due to stenosis, a narrowing of the aortic valve in which its opening becomes impaired resulting in decreased blood flow from the left ventricle to the aorta. Historically, patients would receive a surgically placed valve or medical management. The evolution of percutaneous deployment of an aortic valve allows a large subset of patients who would otherwise not qualify for surgery to have the valve replaced. It also may improve the quality of care of surgically eligible patients by offering a minimally invasive alternative. The PARTNER trial by Edwards Lifesciences has studied transcatheter valves compared to medical management (Cohort B) and compared to surgery (Cohort A).

The market potential for TAVI devices will significantly expand over the next few years.

Data presented at the American College of Cardiology (ACC) conference in April on transcatheter valves were mixed for Edwards Lifesciences, which could be the first to have its transcatheter aortic valve implant (TAVI), Sapien, approved in the US. The Sapien valve's PARTNER results showed higher survival rates with TAVI compared to traditional open-heart surgery, but complications were higher with TAVI treated patients. In spite of the mixed data, physicians continue to expect TAVI valves to be approved. Results below show impressive survival compared to surgery in the short term with a narrowing of the gap over time.

All-Cause Mortality		
	TAVI	Surgery
30-day mortality	3.4%	6.5%
1-year mortality	24.2%	26.8%

Source: PARTNER Cohort A data

Stroke was higher in the TAVI group, but major bleeding was more than twice as high in the surgery group (19.5% vs. 9.3%). Stroke and transient ischemic attack (TIA) are secondary endpoints that continue to be a focus of the medical community.

Stroke		
	TAVI	Surgery
Major Stroke, 30-days	3.8%	2.1%
Major Stroke, 1-yr	5.1%	2.4%
All Stroke or TIA, 30-d	5.5%	2.4%
All Stroke or TIA, 1-yr	8.3%	4.3%

Source: PARTNER Cohort A data

In Cohort A, 698 elderly patients with a median age of 84 and severe aortic stenosis were randomized to either TAVI or conventional surgery among 26 centers, the large majority of which were in the US.

Though stroke was also a focus of the Cohort B trial (versus medical therapy), the stroke rate of Cohort A is lower than it was in Cohort B (2010 data release). Stroke rates seem to decline as surgeons acquire experience. Investigators at study sites quoted a consistent decline in stroke rates and other major vascular complications over time. Dr. John Webb at St Paul's

Hospital in Vancouver claimed that the all-cause vascular adverse event rate at his site is down to 2%, compared to this study's 11% rate.

Among the TAVI patients in Cohort A, 244 were treated using the transfemoral approach, and 104 were treated via the transapical approach. Historically, the transapical approach has been associated with a higher mortality risk, but this study showed as the physicians became used to the technique of the transapical approach, the risk diminished over the three years of the study, indicating risk to be more like the transfemoral approach. This will allow patients with narrow femoral arteries to be treated via TAVI. At one year, deaths in both the TAVI and AVR (aortic valve replacement; surgery) groups were nearly identical, between 25% and 26%.

EW's Sapein device could be approved as early as this fall. Such an approval would likely be limited to high-risk patients. Already, the device is available to such patients at 26 sites from the PARTNER trial.

The degree to which lower risk patients should and will receive Sapien is less clear. *inThought* expects the market to expand slowly.

Cost-effectiveness analysis of TAVI patients was viewed positively at ACC. An analysis of Cohort B patients showed that TAVI is a preferred cost-effective treatment strategy in surgery-ineligible patients. Though TAVI costs approximately \$80,000 more than medical management, the increase in survival associated with TAVI is associated with a cost-effectiveness ratio of approximately \$50,000 per life-year gained. This ratio was viewed as acceptable. An analysis of Cohort A patients showed that TAVI is more cost effective than

surgery as surgery patients were significantly more likely to be hospitalized during the first year follow-up.

**Mitral Valve Repair**

Abbott’s mitral valve clip (MitraClip) was safer than surgery according to two-year data from EVEREST II presented at ACC. However, it was less effective at preventing mitral regurgitation than surgery. The buzz at ACC indicated that the clip will be used in older and sicker patients that are too high risk to undergo surgery. MitraClip also had 78% freedom from surgery at two years. Mortality was similar between the two groups. Although not quite to the extent of surgery, MitraClip did show sustained reduction in regurgitation and LV volumes. Patient symptoms also improved similarly in both groups. Two year results were similar to one year results.

End Point	MitraClip (N=171)	Surgery (N=83)
Freedom from death, mitral valve surgery, and grade 3+ or grade 4+ mitral regurgitation	51.7%	66.3%
Freedom from death	11.0%	10.8%
Freedom from surgery for mitral valve dysfunction	22.1%	3.6%
Freedom from grade 3+ or grade 4+ mitral regurgitation	19.8%	21.7%

Source: EVEREST II data presented at ACC 2011 and Feldman T, Foster E, Glower DG, et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 2011; DOI:10.1056/NEJMoa1009355.

Though there seems to be a patient population for MitraClip, Dr. Sanjay Kaul (Cedars Sinai Medical Center, Los Angeles, CA) was negative on the results, saying a device must be effective first and not just safer. He believes the only population that will use this device are those not suitable for surgery.

Abbott believes otherwise, indicating that the patients’ symptoms improved equally in both groups, and that the MitraClip did provide a sustained reduction in regurgitation. Whether a low level of regurgitation is acceptable is still debatable.

**Ventricular Assist Devices**

A ventricular assist device (VAD) assists the pumping function of the heart. VADs are used to treat patients suffering from heart failure, particularly congestive heart failure (CHF). CHF occurs when the muscles of the heart deteriorate, weakening the pumping power of the heart enough

so that there is not a sufficient level of forward-flowing blood to meet the body’s demands. The deterioration occurs from diseased arteries or valves or a general weakening of the heart muscle. Thoratec has been the leader in VAD systems. The market is broken into bridge-to-transplant and destination therapy patients. Bridge-to-transplant means that the VAD is used to support CHF patients eligible to receive a heart transplant until the transplant is available. Destination therapy means that the device is the last clinical alternative for a chronic patient with end-stage heart failure who is not eligible for transplantation.

Thoratec’s HeartMate XVE and HeartMate II devices are the market leaders in implantable LVADs, and the HeartMate was the first device approved for destination therapy in addition to a bridge-to-transplant. HeartWare has an interesting VAD in development as it is significantly smaller than Thoratec’s devices.

At the International Society of Heart and Lung Transplantation (ISHLT) annual meeting in San Diego last month, HeartWare released combined data from its ADVANCE trial and a continued access protocol (CAP) granted by the FDA in 2010. The combined 250 investigational device patients had survival of 94% at six months, a high rate for these very sick patients. However, blood clot risk was greater than expected; patients had a 9.2% chance of developing a blood clot per year. Inadequate aspirin dosing was blamed for the higher than expected rate.

HeartWare’s device is approved in Europe and Australia. The company completed its PMA submission to the FDA for bridge-to-transplant patients at the end of December. The company is recruiting 50 U.S. sites for a 450-patient destination therapy study. Over 100 patients have been enrolled.

**Impella**

At ACC, and at this week’s Society for Cardiovascular Angiography and Interventions (SCAI) conference, PROSPECT II data provided insight into Abiomed’s Impella 2.5 device. The Impella 2.5 device is a catheter-based, axial-flow pump with a maximal flow of 2.5 liters/min from the left ventricle to the ascending aorta. This “unloading” device can be implanted percutaneously and is used to allow the heart to rest and repair itself. The PROSPECT II study compares, retrospectively,

28,000 patients / year undergoing percutaneous coronary intervention (PCI) with use of an inter-aortic balloon pump (IABP) or Abiomed's Impella 2.5 device. Impella was superior to IABP based on 30% fewer adverse events. At ACC, Impella showed superior hemodynamic support and less support time. Time on the devices averaged 8.2 +/- 2.1 hours for IABP versus 1.9 +/- 2.7 hours on Impella.

The Impella device was FDA approved in 2008. The new 5.0 device should improve outcomes, as it provides more unloading of the heart.

We estimate the market potential for Impella at \$750 million to \$1 billion, based on the intra-aortic balloon pump market. The penetration of this device is still quite low. In fiscal 2009, 521 patients used the Abiomed device. In fiscal 2010, that number increased to 1,649 patients (*Source: ABMD 2010 10-K*). So far, Abiomed has penetrated few than 10% of cath labs.

### Stents / PCI:

The use of stents and PCI in late-stage patients has been declining slightly as medical therapy has shown improved long-term data. In addition, cost benefit analysis of DES has caused declines in DES implantation. The enormous economic burden of these procedures drives study and analysis of their usage.

In the May 4, 2011 issue of the *Journal of the American Medical Association (JAMA)*, a shift in cardiovascular clinical practice was reported. PCI procedures have remained constant while coronary artery bypass graft (CABG) surgeries have declined 38% from 2001 to 2008. Three-year results from SYNTAX trial comparing CABG surgery to PCI has shown that CABG is better than PCI for patients with triple-vessel and left main disease. Major adverse cardiac and cerebral events were also lower in CABG patients. In lower-risk patients, however, PCI is considered a suitable alternative according to the ACC/AHA guidelines. With interventionalists as the gatekeepers to surgery, it is difficult for patients to get to the CABG option with other alternatives available. If patients are being treated earlier, though, PCI may be the suitable alternative.

This year's ACC conference continued to have a significant focus on stents and other revascularization options associated with PCI. The most significant potential treatment change that

may be seen in the coming years is the change from metal stents to a bioabsorbable scaffold, which is being studied by Abbott.

Abbott has set the standard by which drug eluting stents (DES) are measured with its Xience stents. The Xience V stent has set the current benchmark for patient outcomes, with the lowest reported rates of both stent thrombosis and of restenosis.

Abbott's ABSORB and ABSORB EXTEND trials show that its fully bioabsorbable vascular scaffold is safe and effective at one year post implantation. The ABSORB trial enrolled 101 patients. At one year, it demonstrated a 6.9% major adverse cardiac events (MACE) rate and no reports of blood clots. Late loss of 0.27mm is comparable to data seen in drug eluting stents. ABSORB is made of polylactide, a proven biocompatible material that is commonly used in medical implants such as dissolvable sutures.

The PLATINUM trial by Boston Scientific showed that its Promus Element stent, which contains platinum and elutes everolimus, is non-inferior to Abbott's Xience V stent. This late breaking clinical trial session data was received with some controversy. This new stent, which received CE Mark approval in 2009 and expects FDA approval in 2012, uses platinum instead of cobalt in the scaffolding. This is thought to make it more flexible yet strong. The stent uses the same drug (everolimus) and polymer as the Xience V, a change from Boston Scientific's initial paclitaxel-eluting stent.

One year results were reported from this five-year trial. The PLATINUM study follows 1,530 patients at 132 sites worldwide. Patients were randomized to either the new platinum stent (n=768) or the cobalt stent (n=762). Target lesion failure (TLF) is the primary endpoint. At 12 months, TLF was 3.4% in the Promus stent group and 2.9% in the Xience V group. There were no significant differences between the two in other safety and efficacy measures, including stent thrombosis, which occurred in just 0.4% of patients in each group.

Medtronic's RESOLUTE US trial one year data was also released at ACC. Medtronic's new Resolute stent had lower rate of restenosis at one year compared to the company's predecessor stent, Endeavor. Resolute uses the same stent design and drug (zotarolimus) as Endeavor, but a different

polymer is used to bind the drug to the stent. The polymer used on the Resolute stent lengthens the drug release out to three months.

RESOLUTE US enrolled 1,402 patients and all were treated with the Resolute stent. One year results were compared with historical results. The primary endpoint was target lesion failure (TLF). At one year, TLF in the Resolute patients (stent size 2.5 to 3.5mm in the main cohort) was 3.7%, compared with 6.5% in historical controls. Event rates were

0.4% for cardiac death, 1.3% for target vessel MI, and 2.0% for target lesion revascularization, which is on the low side but within the range of historical trial data.

Resolute is viewed as very effective. The RESOLUTE trials enrolled a high percentage of diabetics, and physicians seem to view Resolute as a stent for complex situations such as diabetes, multivessel disease, or high-restenosis situations.

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