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NEWS RELEASE

January/February 2011



[From the Desk of Ivan Vesely, Ph.D.](#)

Dear Colleagues

We hit the ground running in January. Having received some important funding towards the end of 2010, we spent the majority of December finalizing our plan to begin our "First-in-Man" studies (FIM) with our surgically implantable Vitality™ Valve. Please see the [ValveXchange home page](#) for a count-down clock to FIM. The key resources that enable us to execute this plan include two new executives - [Todd Campbell](#), Senior Executive Director of Product Development, and [Kevin Morningstar](#), Senior Director of Quality and Regulatory Affairs. Both of these gentlemen's bios are highlighted in this issue of the Newsletter. This month's Reality Check piece reviews new advances in regulating TAVI - it would appear that The Age of Reason is finally upon us.

For those new to this Newsletter, ValveXchange is an emerging technology company based in Colorado. We call ourselves "The Lifetime Tissue Valve Company" and are developing the first-of-its-kind "serviceable" bioprosthetic valve. By offering periodic, minimally invasive exchange of the worn-out leaflet set, young and physically active patients can avoid the use of a mechanical valve and the associated Coumadin® anticoagulation therapy. By adhering to the time-proven design tenets of conventional bovine pericardial valves, we believe that the ValveXchange system will offer the best combination of least-invasive techniques and greatest valve longevity and durability.

Press Release

Valve Industry Veteran, Todd Campbell, joins ValveXchange as Senior Executive Director of Product Development.

January 17, 2011. Denver - ValveXchange Inc. is pleased to announce that Mr. Todd Campbell has joined the VXi team to direct product development and help the company achieve its First-in-Man (FIM) milestone. Todd Campbell is a Medical Device Industry professional, technical visionary, entrepreneur, leader, and is skilled in operations, project management and executive leadership in the development of life saving medical devices. Todd was the first to join ValveXchange many years ago when Dr. Vesely founded the company; while both were developing the exchangeable valve concept on a part-time basis. Mr. Campbell served as the Principle Investigator on ValveXchange's first 2 NIH SBIR grants, and continued to work with ValveXchange through its recent scale up in R&D efforts. Over the past two years, Mr. Campbell and has been instrumental in establishing the valve assembly methodology, the procurement of pericardium, Dacron[®] and suture material, and the training of assembly technicians. With ValveXchange now moving toward a "First-in-Man" study during 2011, Todd Campbell has joined the Executive Team of ValveXchange on a full-time basis to take on the role of Senior Executive Director of Product Development.



Todd's career spans over 30 years, with most of his effort in the bioprosthetic heart valve field. He has held Operations, R&D, Regulatory and Quality roles for several heart valve and cardiovascular companies including Hancock Laboratories - the first US manufacturer of bioprosthetic valves; St. Jude Medical, where he managed tissue technologies and bioscience; and Sadra Medical - a percutaneous heart valve start-up company (acquired by Boston Scientific) as their VP of Research and Development and co-Chief Operations Officer. At Sadra, he led the redesign of the valve and took it to its First-in-Man study. He also served as VP of R&D for Hansen Medical during the time that they were developing the AorTx transcatheter valve technology. Todd previously held R&D roles at Medtronic AVE as Senior R&D Engineer where he managed the development of novel coronary stent and catheter technologies incorporating molecular, cellular and biological therapies for treating arterial, coronary and vascular diseases. Mr. Campbell founded and led Medtronic's initial effort in drug eluting stents and pioneered the initial studies into biodegradable stent technologies as alternatives to conventional drug-eluting stents. As Sr. Research Chemist and COO of Tissue Implants at Baxter (Edwards) Healthcare, Todd developed anticalcification treatments to improve the clinical longevity of bioprosthetic heart valves

Mr. Campbell received his undergraduate degree in Biological Sciences from the University of California, Irvine and his graduate degrees in

Molecular Biology and Engineering from California State University, Fullerton. Mr. Campbell has been involved with entrepreneurial start-up organizations over the last 10 years. His efforts have been recognized by Popular Science, with the award of best new medical device in 2003 (for the HemCon® Bandage) and also recognized by the US Army for best new medical device in 2004. Mr. Campbell is named inventor on twenty-five patents and patent applications, with twelve of these in the cardiovascular and interventional cardiology field. Mr. Campbell is the recipient of two NIH SBIR grants for heart valves and two Medtronic Corporate Quest grants for advanced stent designs. He has authored multiple strategic business plans for entrepreneurial companies, and founded Millipede® (military and civilian podiatry devices) and Endolumen Therapeutics (vulnerable plaque devices). Mr. Campbell continues to be involved in International organizations providing expert sourcing of bovine pericardium from GBR 1 countries (Australia and New Zealand), and professional consulting to medical device companies in China, Thailand, Australia and Israel.

Medical Device Industry Veteran, Kevin Morningstar, joins ValveXchange as Senior Director, Regulatory Affairs and Quality Assurance.

February 14, 2011. Denver - ValveXchange Inc. is pleased to announce that Mr. Kevin Morningstar has joined the VXi team to direct the regulatory compliance program. With ValveXchange now moving toward a "First-in-Man" study during 2011, Mr. Morningstar has joined the Executive Team of ValveXchange on a full-time basis to take on the role of Senior Director, Regulatory Affairs and Quality Assurance.



Mr. Morningstar has over 25 years experience in regulatory affairs and quality assurance in the medical device manufacturing industry. He began his medical device career in 1983, and has held positions in Operations, Engineering, Regulatory Affairs, Quality Assurance, and Executive Management. He has extensive on-the-job experience with medical devices used in cardiology, neurosurgery, anesthesiology, and nephrology. His cardiac device experience includes cardiopulmonary bypass equipment, implantable cardiac pacemaker leads and programmers, digital stress echo systems, 3-D and 4-D digital cardiac imaging, aortic balloon pumps and catheters, and endocardial laser catheters. Prior to creating his own regulatory consulting practice in 1997, Mr. Morningstar held engineering, regulatory, and management positions with TomTec Imaging Systems, Ohmeda, Telectronics Pacing Systems, and COBE Laboratories. He also co-founded Silverglide Surgical Technologies, Inc., a surgical instrument business successfully sold to Stryker Corporation in 2006 in a planned exit strategy. He is a seasoned engineer, manager, entrepreneur and investor.

Mr. Morningstar has a broad depth of experience with FDA regulatory requirements for medical devices, for both product marketing approvals and quality systems compliance. He is also very knowledgeable with

respect to corresponding European and Canadian medical device requirements. Over the years he has worked on many Section 510(k) Premarket Notifications, Premarket Approval Applications, and European CE Mark Applications. He has broad experience in quality system architecture, process development, design assurance, quality system audit, FDA inspections, international standards conformance, promotional material, labeling, risk management, medical device recalls, adverse event reporting, process validation, employee training, and production and process control.

Mr. Morningstar received his undergraduate degree in Electrical Engineering from Michigan State University in 1980. In 1984 he became a Registered Professional Engineer in the State of Colorado. He earned a Regulatory Affairs Certification from the Regulatory Affairs Professionals Society in 1992 and became a Certified Quality System Auditor in 1993. In 2005 he earned a Certificate in Production and Inventory Management (CPIM) from APICS. Mr. Morningstar is named co-inventor on two patents in the electrosurgery field. He is a seasoned speaker and instructor, and continues to be involved in regulatory consulting to medical device companies in the U.S. and Europe.

Technology Report

Transapical Leaflet Exchange

ValveXchange was founded on the principal of *"Offering heart valve patients of all ages the best possible quality of life and freedom from complications"*. We do that by incorporating clinically proven heart valve design features into innovative products to achieve the best possible durability, safety, hemodynamic performance and least invasiveness.

Our motto *"The Lifetime Tissue Valve Company"* is made possible through leaflet exchangeability and valve renewal. Least invasiveness is enabled by exchanging the leaflets through an off-pump, transapical approach. This has been the "Holy Grail" for our company, and we are one step closer to achieving that goal.

Transapical leaflet exchange requires two technologies to operate in concert with each other. The first is a valve design that can actually be exchanged successfully. That exchangeability feature has been demonstrated through many open, on-pump animal experiments over the past two years. The tools and the technique to do so are now refined to the point that even a non-surgeon like myself can swap out the leaflet set in less than two minutes. Even in the absence of a transapical tool set, a surgeon could do the leaflet exchange through a very small incision, with just a few minutes of cross clamp time - a huge advantage to patients with tissue valves.

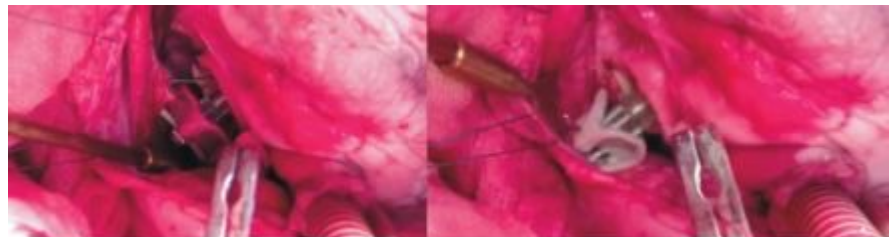
The second technology is access to the valve through the apex of the heart, off pump. That technology was demonstrated in September of last year and reported upon in our [October newsletter](#). In two separate

experiments, we used the transapical tool and its introducer to deliver the transapical Vanguard™ into the aortic root of the sheep, on a beating heart. Through those studies, and that experience, we have adapted our open-exchange tools, and created a multi-function tool that enables the exchange to take place through the apical access route.

These two technologies were then integrated into a functional transapical leaflet exchange tool. Our first attempt at a fully transapical leaflet exchange took place earlier this year in the labs of [Professor Richard Bianco](#) in the [Experimental Surgical Services Department](#) of the University of Minnesota. Indeed, we have worked with Dr. Bianco on the majority of our animal experiments since we began developing and testing our exchangeable valve product line. Dr. Bianco has an excellent team of young veterinary surgeons and technicians that do their utmost to execute the animal study for the best possible outcomes.

During this first-ever transapical leaflet exchange study, we implanted the Vitality™ valve using the conventional open surgery approach, as would be done in human patients. With the animal still on pump, we then opened the apex and inserted our transapical exchange tool. We left the aortotomy distal to the valve open, so that we could record video images of the tool from the outflow aspect, as it removed the original leaflet set and attached a new one.

The procedure went remarkably well. The tool engaged the leaflet set and exchanged it in just a few minutes. The images below show the process of the old leaflet removal and collapse, and the installation of the new leaflet set.



Removing original leaflet set

Attaching new leaflet set

After the leaflet set was exchanged, the heart was restarted and the new leaflet set worked flawlessly. We are thus happy to report that the feasibility of transapical leaflet exchange has now been demonstrated.

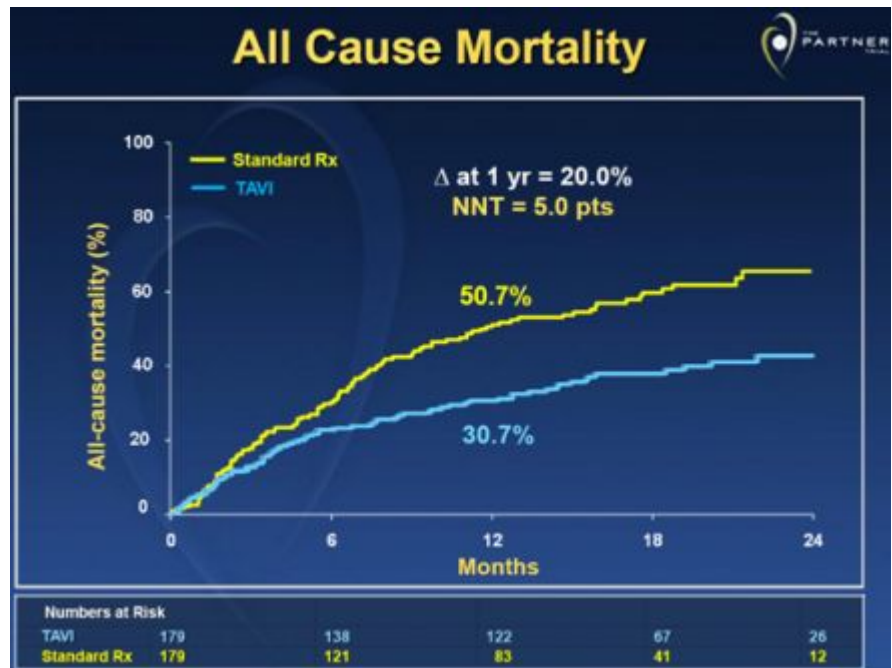
Reality Check

TAVI, PARTNER and VARC: The Age of Reason is finally upon us.

On the heels of the tremendous success of the PARTNER trial, TAVI pundits have been speculating on the rapidity by which transcatheter aortic valve implantation (TAVI) will supplant conventional surgical aortic valve replacement (SAVR). Depending on how one looks at the

complexity of implementing TAVI as a routine treatment for aortic stenosis, the procedure volumes may skyrocket in just a few years, or they may be quite modest.

What has become certain is that the PARTNER trial has set a new standard for the quality of execution of a Clinical Study. The quantitative differences in outcomes between patients receiving the Sapien[®] valve and those treated with Standard Therapy were indeed remarkable. The mortality differences between the two groups were stunning - TAVI having reduced the 1-year mortality from 50% to 30% (see slide below).



Another way of looking at the data is like this - the huge difference between the two test groups means that it does not take very many people to be treated to get a measurable difference. Indeed, one needs to treat only 5 patients with TAVI in order to be sure that at least one life was saved at the one-year time point. This is far, far better than what is typically shown for pharmacological trials in which thousands of patients are needed to demonstrate a difference in the efficacy of a new drug; the benefit being only a few percent better than the control.

Details of the PARTNER trial were published in the [October issue of the New England Journal of Medicine](#). Some of the positive conclusions of PARTNER were:

- (i) Standard non-surgical therapy for treating severe aortic valve stenosis, which included balloon valvuloplasty, did not alter the natural history of severe aortic stenosis - 50% of the patients still died at one year.
- (ii) Transfemoral TAVI was better than standard therapy, reducing the rate of death and repeat hospitalization.

(iii) Patients who underwent TAVI did not have significantly greater rates of death in the first 30 days of treatment than those who received standard therapy. This means that even as an experimental procedure, TAVI did not trade off a long-term benefit for increased short-term mortality risk.

(iv) Patients had a significant reduction in symptoms after TAVI, meaning that they were in a clinically better condition.

On the negative side, the PARTNER trial also demonstrated that:

(v) Patients undergoing TAVI experienced more strokes and cardiovascular complications than those undergoing standard therapy. This means that there really was compromise between ultimate survival and procedural complications that diminished the quality of life in some patients.

(vi) TAVI was accompanied by frequent occurrence of paravalvular leaks and regurgitation that rarely required further treatment. Again, severe stenosis was fixed, but at the expense of an imperfect outcome, at least when compared to the expectations that one might have with Surgical Aortic Valve Replacement (SAVR).

However, the resounding conclusion from the PARTNER trial was that

Balloon-expandable TAVI should be the new standard of care for patients with aortic stenosis who are not suitable candidates for surgery!

Immediately afterward, the web came alive with speculations as to how TAVI will impact the future of aortic valve procedures in general. How can we expand the indications for TAVI to a less sick group of patients? How can we treat all patients with TAVI?

But not everyone is a TAVI pundit. Immediately after being reported in the New England Journal of Medicine, the PARTNER trial data got some immediate push-back by way of several [Letters to the Editor](#). In the first letter, Dr. [Rita Redberg](#) from UCSF, a noted expert in Health Policy and Technology Assessment, challenged the validity of the control group, commenting that balloon valvuloplasty was a "discredited procedure" that was "discontinued years ago" because of "dismal 40% event-free 1-year survival". Dr. Redberg concluded her letter stating that "Unfortunately, the PARTNER study did not include a valid control group, and thus we do not know how TAVI compares with standard therapy".

The second letter from Drs. Trippoli and Messori, from Florence, Italy, questions the similarity of the two groups, commenting that patients undergoing "TAVI had a significantly better logistic ... EuroSCORE than those receiving standard therapy (26.4±17.2 vs. 30.4± 19.1, P=0.04)", again, questioning whether TAVI was truly better than Standard Therapy.

The third letter from Drs. Newman and Shimbo, from Columbia University, comments on the cost effectiveness of TAVI, stating that "...Given the demonstrated increase in periprocedural strokes and bleeding

complications, future investigations should consider the cost-effectiveness of TAVI and the patient's quality of life after this procedure, especially in patients at elevated, but not prohibitive, surgical risk."

In his rebuttal, Dr. Leon, the [author of the PARTNER report](#), defended the use of balloon valvuloplasty as "an entirely valid control group in the randomized PARTNER trial" stating that it was safe and led to a 20% reduction in mortality when compared to those patients who did not get balloon valvuloplasty as part of their "standard therapy". He dismissed the randomization concerns by stating that "In a small, randomized trial such as PARTNER such baseline disparities are commonly observed, and after adjustment for baseline risk imbalances, there were still marked differences in the mortality end point between the test and control therapies." Finally, regarding quality of life measures, Dr. Leon commented that "quality-of-life measures were observed; these results favored TAVI over standard therapy at 1, 6, and 12 months," but admitted that "Cost-effectiveness analyses from the PARTNER study are ongoing."

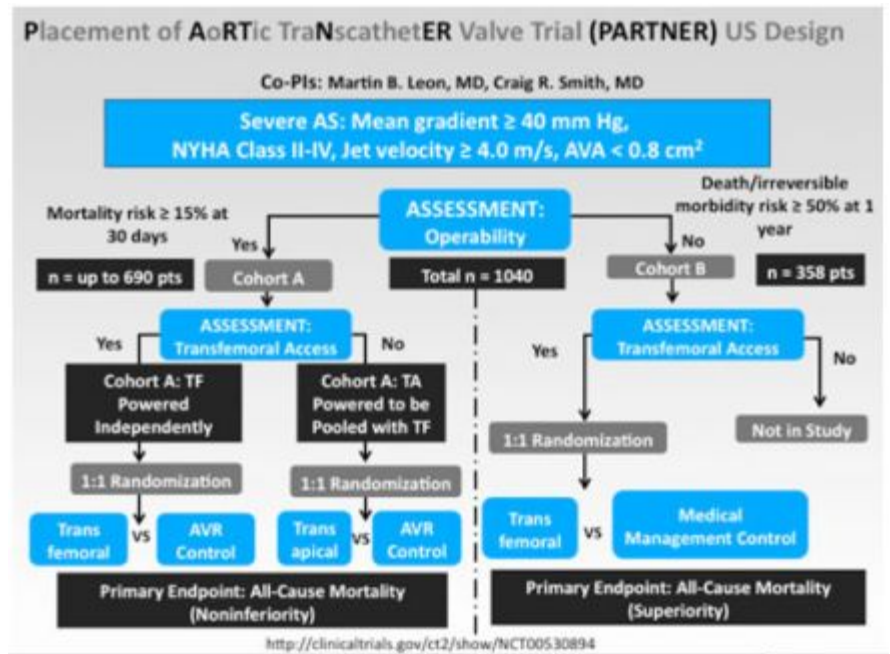
So in the minds of some people, the outcomes of the PARTNER trial are not a "Slam Dunk". The issue of operability of the patients remains questionable to some, and cost effectiveness remains a huge, unanswered question. Indeed, one of the PARTNER trial investigators commented to me privately that many of the TAVI group patients were so sick that it might have been better to just leave them alone. One must thus question whether that lovely, funny, spry old woman that was [brought up on stage at the TCT](#) was an exception and not the rule of what a typical TAVI patient looks like. TAVI may prolong the life of some people, but at what cost and societal impact?

Even though the PARTNER trial data has spoken, there are still many ways to interpret the words. Those that want to focus on extending healthy lives will focus on the positives. Those who are focused on cost containment will point out that TAVI does not help curb our medical cost problems, and those that are just plain skeptical will remain skeptical.

What I find so interesting in all this is the way that the FDA has responded. Even before the PARTNER trial data came out, the FDA was reconsidering its position on randomizing patients between TAVI and standard therapy. That position was solidified shortly afterwards, as the FDA had Medtronic [remove its randomization component from the sickest of its patients](#). In other words, with the PARTNER trial data in hand, it would be difficult to justify randomizing a really sick patient between TAVI and standard therapy - TAVI does offer a clear therapeutic benefit for these really sick patients. The FDA thus believes that the PARTNER trial was executed sufficiently well as to warrant the removal of the randomization from similar subsequent trials on an ethical basis.

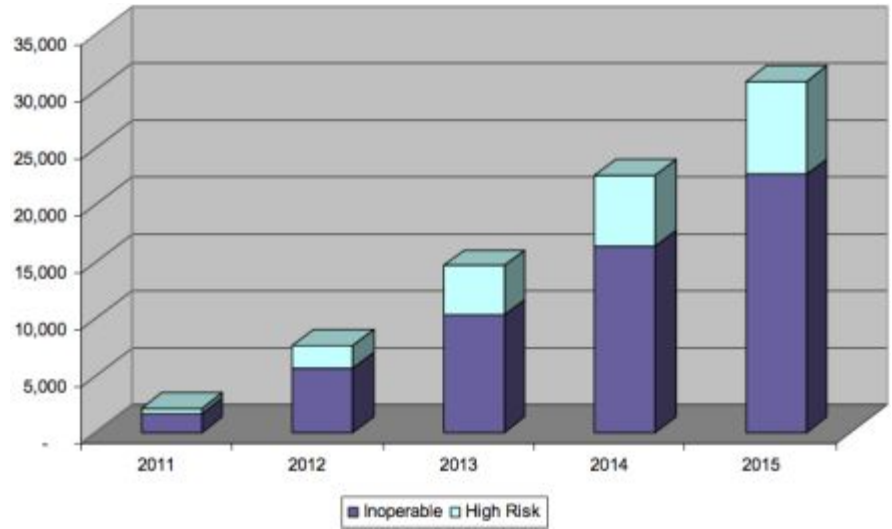
Having said that, it now needs to be appreciated that those companies that follow in the footsteps of PARTNER and have products that aim to compete with the Sapien[®] valve, have a higher bar to jump over. Since the Medtronic / CoreValve [SURTAVI trial](#) will not be allowed to randomize the sickest of the patients, Medtronic will not have the benefit of showing how the CoreValve[®] improves outcomes relative to Standard Therapy. By not being first like Edwards, no other company will have the luxury of

basking in the glory of showing how their cool new transcatheter valve saves lives over Standard Therapy. Indeed, what everyone will be looking for is how well the CoreValve[®] device meets the performance standards set by the Sapien[®] valve. Although it is not an objective of the trial, the world will be watching to see if CoreValve[®] matches the clinical outcomes of the Sapien[®] valve in these very sick, inoperable patients. Given that the [CoreValve has always had a greater incidence of conduction anomalies and need for pacemaker](#) this will be an interesting horse race indeed.



But the PARTNER trial is not over yet. Only the first half (see chart above) has been revealed. How TAVI does against surgery is planned to be revealed in April of this year at the [ACC i2 Summit in New Orleans](#), when the PARTNER Cohort A data is reported. The Cohort A component randomized patients not against "Standard Therapy", which many believe is really "doing nothing", but against the current gold standard which is conventional open surgical aortic valve replacement (SAVR). Keep in mind that the clinical sites chosen for PARTNER are some of the best centers in the world - Columbia Medical Center, The Cleveland Clinic, The Mayo Clinic, Stanford, to name just a few. The surgeons performing SAVR as part of this trial are thus not the average surgeon, but the best of the best. Their outcomes are thus likely to be outstanding. Unlike the "superiority" criterion for Cohort B that was statistically so clear, a "non-inferiority" criterion is harder to demonstrate statistically.

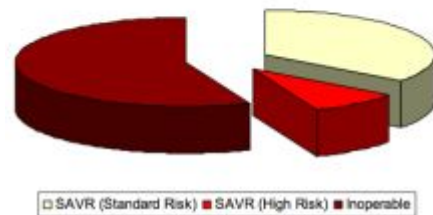
Nevertheless, TAVI works exceedingly well in the old, inoperable patient - that has been shown through the PARTNER Cohort B data. Accordingly, some believe that TAVI procedures will continue to grow exponentially and eventually replace valve surgery.



Perhaps the most complete and authoritative report on the future of heart valve technologies is by [Health Research International](#). That report shows a healthy increase in TAVI volume to about 30,000 procedures per year in the US by 2015 (see image above). These estimates are based on the following assumptions:

The number of patients in the US that suffer from Severe Aortic Stenosis is 550,000. This is based on a 0.6% prevalence in the adult population estimated by [Nkomo et al.](#) Interestingly, these huge prevalence numbers indicate that only about 15% of all patients suffering from AS actually get treated by way of a prosthetic heart valve. Health Research International (HRI) stands by these numbers, arguing that *"these data suggest the majority of patients are undiagnosed, are asymptomatic, are not being referred or are refused for valve replacement surgery, or a combination of these factors."* From this very large number, HRI then assumes that 56% are classified as inoperable, according to a compilation of clinical papers, and ultimately comes up with a conclusion that in 2008 there were 116,770 patients in the US that could be classified as candidates for TAVI (see table right). The 30,000 TAVI procedures estimated for 2015 is thus based on a *"modest 20% penetration"* of this candidate market. HRI then assumes that *"about half of such patients also require CABG and, thus, will not be considered for TAVI. The net effect will be expansion of the treated patient population and a minimal cannibalization of the SAVR caseload of less than 10% in 2015."*

Population	Patients
Severe Aortic Stenosis Patients	536,755
% referred for surgery	34.1%
Surgical Candidates	180,365
% inoperable	56.2%
Inoperable Patients	101,365
% undergoing surgery	43.8%
SAVR Procedures	79,000
% high risk	19.5%
High Risk SAVR Patients	15,405
TAVI Candidates	116,770



So on one hand, one can be very conservative and assume a low penetration rate of TAVI into the SAVR domain - about 10%, but on the other hand, one can be very liberal and estimate what is essentially an epidemic of Severe Aortic Stenosis with only 15% of all patients being treated. Is this realistic? Is there some basis on which to assume that TAVI can somehow cure this "epidemic" and bring these previously untreated or untreatable patients into the current health care system?

Well, given that over [50 million Americans don't have health insurance](#), that US health care costs continue to increase, and that there is a movement to actually reduce health care costs, the assumption that we can now treat 6 times more patients with aortic valve stenosis is somewhat "against the current". Moreover, with transcatheter valves prices expected to be \$22,000 in 2011, increasing to almost \$25,000 by 2015 (according to HRI), it is difficult to expect that payers will reimburse them without a fight. Indeed, [Wellpoint of South Carolina has issued a policy statement that effectively denies reimbursement for Sapien TAVI procedures](#), [Blue Cross / Blue Shield of North Carolina will NOT pay for TAVI](#), [Anthem Blue Cross of California considers TAVI "not medically necessary"](#), and the country of [Belgium has not reimbursed, nor approved TAVI](#) since the start when transcatheter valves first received CE Mark approval. Indeed, currently, we are aware of only five European countries that have approved the use of TAVI - [France](#), the [UK](#), Germany, [Italy](#) and [Spain](#). How quickly TAVI will become reimbursable around the world remains to be seen.

Certainly, in the US reimbursement is known to lag adoption, and eventually comes around once clinical benefit is shown. Benefit is shown by lots of good clinical data and the PARTNER trial is a good start. Representatives from the FDA were at the TCT where the PARTNER cohort B was presented, and were certainly congratulatory. But at the same time, the FDA made it quite clear that approval will come with lots of strings attached. For one, TAVI will not be simply handed over to any eager cardiologist who wants to do it. There will likely be accreditation and competency requirements, and very strict inclusion/exclusion criteria. One PARTNER trial investigator commented that perhaps an additional 10% patients could be appropriate candidates for TAVI, if all the criteria used for the PARTNER trial were to be adopted in clinical practice. This number was later confirmed by other talks at the recent [STS meeting in San Diego](#). Additionally, there are indications already that the companies themselves have been restricting the dissemination of TAVI to cardiologists with limited TAVI experience for fear that clinical outcomes will be compromised.

So on the high end, we have 116,770 additional patients as candidates (from HRI table above). On the low end we have an additional 10% of the current SAVR group (79,000) or less than 8,000 additional patients per year in the US. This is clearly a huge spread in the number of projected clinical procedures. The truth most likely lies somewhere in between, and is highly dependent upon (i) the restrictions that will be placed on which patients receive transcatheter valves, (ii) what level of expertise a physician or a clinical center must have in order to qualify as a TAVI site, and (iii) how well TAVI will be reimbursed and whether clinics will implant them in advance of reimbursement.

A decade ago, transcatheter valves were born from the fire of controversy. Interventional cardiologists loved them instantly and many surgeons began to hate them just as fast. Many viewed TAVI as perhaps the worst example of an in-elegant, brute force, technological approach that, like intracoronary stents, would supplant an elegant, artistic craft perfected over decades - an imperfect solution devised solely for the purpose of moving the incision to where it cannot be seen.

But that was before the PARTNER trial. PARTNER changed the world. From the outset, PARTNER was a true "partnership" between cardiologists and surgeons. The cardiologists may have won, but the surgeons did not lose. The PARTNER trial demonstrated that new technologies could indeed be judged objectively, critically, transparently and collaboratively.

If TAVI begot PARTNER, then PARTNER begot VARC. As described in a [recent publication, VARC](#) (the Valve Academic Research Consortium) *"established an independent collaboration between Academic Research organizations and specialty societies (cardiology and cardiac surgery) in the USA and Europe. Two meetings... were focused on creating consistent endpoint definitions and consensus recommendations for implementation in TAVI clinical research programs. Important considerations in developing endpoint definitions included: 1) respect for the historical legacy of surgical valve guidelines; 2) identification of pathophysiological mechanisms associated with clinical events; 3) emphasis on clinical relevance. Consensus criteria were developed for the following endpoints: mortality, myocardial infarction, stroke, bleeding, acute kidney injury, vascular complications, and prosthetic valve performance. Composite endpoints for TAVI safety and effectiveness were also recommended."*

This publication from the outset admits that *"the explosive growth of TAVI has created a 'clinical data conundrum': investigators were not prepared to optimally organize and interpret clinical data for this radically different treatment, rendering thoughtful assessment of clinical trial outcomes difficult and inter-study results comparisons problematic."* When reading this publication, I was particularly impressed with the recommendation that TAVI should be compared to surgical aortic valve replacement, specifically by measuring "all-cause mortality" and "device durability for the life of the implant". This is totally new. To date, there have been well over 10,000 transcatheter valve implants, yet the number of explanted valves and pathological exams numbers in the dozens. The most noted transcatheter valve pathologist has examined less than a dozen explanted valves. Why? Apparently when old people die with a transcatheter valve, few are interested in finding out why - autopsies are just not done. Few apparently ask the question *"Did the transcatheter valve kill the patient or was it the underlying patient co-morbidities?"* Perhaps now, under the VARC guidelines, such questions will be more commonly asked and rigorously addressed.

Besides (i) all-cause mortality, the VARC guidelines also specify the reporting of (ii) myocardial infarction - both peri-procedural and late, (iii) stroke - both the severity and the etiology, (iv) bleeding events and their severity, (v) the occurrence of acute kidney injury, and (vi) vascular complications, such as aortic dissections or access site injury and the

need for surgical correction. Most interesting was the inclusion of "*Prosthetic valve associated complications*". These are those that are caused by the introduction of the prosthesis, such as conduction abnormalities, coronary artery obstructions and over the longer term, [Prosthesis-Patient Mismatch](#) (PPM). Finally, the VARC recommendations embraced the concept of measurable "Clinical Endpoints". Again, taking guidance from the experience of surgically implantable valves, the new way of evaluating the effectiveness of transcatheter valve therapy will be based on a composite of a number of measurable criteria, such as (i) has the patient's frailty been reduced? (ii) was there a conversion to surgery? (iii) was there a re-intervention, like a valve-in-valve?

Many of the complications associated with TAVI that were dismissed in the early days as "part of the learning curve" have clearly remained (i.e., [vascular complications](#)). Those will now be catalogued and compared to the real standard therapy which is, and always has been, Surgical Aortic Valve Replacement (SAVR). Eventually, new transcatheter valves will likely be approved using a formula that worked very well for surgically implantable valves - Objective Performance Criteria (OPCs). For surgical valves, these OPCs have been specified based on several decades of experience with surgical valves. Historical precedents are thus the "control group" against which new surgical valves are judged. To get a new surgical valve approved, one must show "non-inferiority" to the historical control group, which is non-inferiority to the published OPCs (see table below).

	Rigid	Flexible
Thromboembolism	3.0	2.5
Valve thrombosis	0.8	0.2
All hemorrhage	3.5	1.4
Major hemorrhage	1.5	0.9
All paravalvular leak	1.2	1.2
Major paravalvular leak	0.6	0.6
Endocarditis	1.2	1.2

NOTE—Values are in % per valve-year.

As an example, a new surgical valve cannot have an incidence of paravalvular leak any greater than two times the published OPC of 1.2%. Why? So that patients don't get "Buyers' Remorse" a few years later by having a cool new valve that trades off some benefit for some underlying flaw. Presumably, it would not be a good thing if a valve has better hemodynamics and greater Effective Orifice Area at the expense of paravalvular leak, for example. This is exactly why the Edwards Magna - a valve that does indeed have better EOA than its Perimount predecessor still had to satisfy the published OPC's by way of a [clinical trial](#). Just because a valve has better EOA does not give it the excuse of having other flaws.

Similarly, a transcatheter valve that is implanted without surgery into younger people should not trade off the benefit of an off-pump implant

approach in exchange for a huge new problem of paravalvular leaks, or more importantly - durability. The FDA, the broad clinical community and informed patients themselves are unlikely to tolerate such trade-offs, and transcatheter valves will most likely need to meet the same, or nearly the same OPCs as do surgical valves today.

Outside the US, "buyers remorse" may be happening already. There have been anecdotal reports that somewhere in Europe, a 45 year-old patient demanded that he get a CoreValve, and he did. Reportedly he paid for it and some European cardiologist implanted it. Whether true or not, such cases will occur somewhere and set up the conditions for heart valve buyer's remorse. Five to seven years later, the valve will likely fail and that patient will be faced with two not so pretty options - (i) get the valve surgically reoperated and have a proper surgical valve implanted or (ii) get a valve-in-valve procedure.

If he chooses the first option, he will now face a far more complicated, more prolonged and more risky surgery to have the original valve dug out of the aortic root, since much of the metal in contact with the aorta has been shown [to grow over with pannus](#) (click [here](#) for additional reference). Not only did he postpone the inevitable surgery, but he made it more complex. Its like paying off one credit card debt with another credit card.

If he chooses the second option, he will have a smaller EOA and will postpone the inevitable by another 5-7 years. By then, option (ii) will no longer be available and surgery will need to be done anyway. And as he lives with the transcatheter valve, this young man will expose himself to thrombosis risk, he'll need to be on Plavix[®], he'll have a diminished exercise tolerance because of the mild to moderate perivalvular leak as well as PPM, and so forth. This is essentially what the FDA wants to avoid happening in the US. In the US we don't tolerate Buyer's Remorse very well. We sue people and we complain to the FDA. The FDA will succeed in limiting the dissemination of TAVI and VARC is going to help it. [The FDA is clearly supportive of the VARC statement.](#)

TAVI will not be a repeat of what happened with intracoronary stents. In the words of [Dr. Blase Carabello](#), who so eloquently put it in a [recent editorial on TAVI](#) - "*Will we let the genie out of the bottle again as we did with percutaneous coronary intervention, when some procedures were performed without clear cut indications or even clear cut benefits? Let us keep the genie in the bottle this time around and make the field of percutaneous valves one of clinical, ethical, and therapeutic envy for the rest of medicine.*"

I am beginning to think that the PARTNER trial and VARC in particular, will make that aspiration become a reality.

Closing:

Perhaps we are finally learning from history. Unlike intracoronary stents, heart valves have decades of clinical experience. We know pretty well what causes tissue valve failure over time, and we know that time is shorter in younger, more active patients. We know that long-lived valves

need to subscribe to the ["three tenets of good valve design"](#). Current generation transcatheter valves do not. PARTNER and VARC argue for reason and evidence in heart valve clinical testing and application. Perhaps the Age of Reason is finally upon us.

Sincerely,

Ivan Vesely, Ph.D.
Founder and Chief Scientific Officer
ValveXchange Inc.
ivesely@valveXchange.com

Recent News Releases

October, 2010. Denver - ValveXchange Inc. is pleased to announce that Blase Carabello, M.D., has joined the VXi Medical Advisory Board. [Read More.](#)

October, 2010. Denver - ValveXchange Inc. is pleased to announce that Bonnie Vivian has joined the VXi Board of Directors. [Read More.](#)

September, 2010. Denver - ValveXchange Inc. is pleased to announce that Carlos Ruiz, M.D., Ph.D., has joined the VXi Medical Advisory Board. [Read More.](#)

August 19, 2010. Denver - ValveXchange Inc. is pleased to announce the receipt of a \$1.3 million Small Business Innovation Research (SBIR) grant from the National Institutes of Health (NIH) under the Fast Track program. The Fast Track program is reserved for highly innovative and competitive projects with a short time-line to commercialization. This is VXi's 5th NIH SBIR Grant.

June, 2010. Denver - ValveXchange Inc. is pleased to announce that Lars G. Svensson, MD, PhD, has joined the VXi Medical Advisory Board. [Read More.](#)

April 13, 2010. Minneapolis - Dr. Ivan Vesely, the founder of ValveXchange Inc., presented a review paper entitled "The Three Tenets of Good Valve Design: Where transcatheter Valves Fail", at the 2010 [Design of Medical Devices conference](#) in Minneapolis, Minnesota. Other noted invited speakers were Manny Villafona, the founder of St. Jude Medical, and Dr. Robert Levy, a pioneer in understanding prosthetic valve calcification. Dr. Vesely's presentation can be viewed [here](#).

January, 2010. Denver - ValveXchange Inc. is pleased to announce that it has received a \$250,000 grant from the State of Colorado under the Bioscience Discovery Evaluation Grant Program (BDEGP). [Read More.](#)

November 19, 2009. Aurora, CO - ValveXchange Inc. recently executed a license agreement with the University of Colorado for a process to

transform cardiac imaging data into high-quality three-dimensional models used for heart valve product development, clinician training, and pre-procedure planning. [Read More.](#)

October, 2009. Denver - ValveXchange Inc. is pleased to announce that Dr. Antonio Calafiore has joined the VXi Medical Advisory Board. Dr. Calafiore is recognized internationally for pioneering off-pump coronary artery bypass grafting and the "Calafiore technique" of myocardial preservation. Dr. Calafiore has recently moved from Italy to Riyadh, Saudi Arabia as the director of the Prince Sultan Cardiac Center. [Read More.](#)

September, 2009. Denver - ValveXchange Inc. is pleased to announce that Michael J. Mack, M.D., has joined the VXi Medical Advisory Board. Dr. Mack is Director of Cardiovascular Research and Cardiovascular Medicine of the Heart Hospital Baylor Plano and Director of Cardiovascular Surgery for the Baylor Healthcare System. He is considered to be the most noted authority on the emerging field of transcatheter valves. [Read More.](#)

June, 2009. Denver - ValveXchange Inc. announces that Walter Randolph "Randy" Chitwood, Jr., M.D., FACS, FRCS has joined the VXi Medical Advisory Board. Dr. Chitwood was the principal investigator of the FDA robotic mitral valve trials that led to approval for this use in the United States. Today, he is the world's leader in robotic mitral valve surgery. [Read More.](#)

