

In This Issue

[Press Release](#)

[Other News](#)

[Reality Check](#)

[Previous News Releases](#)

About Us

- [Company](#)
- [Products](#)
- [Legal Notices](#)
- [Contact Us](#)

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Notice:

ValveXchange, Inc. products have not been approved by the U.S. FDA or any other Regulatory Agencies. This newsletter contains forward looking statements which represent management's best judgment, but are speculative and may not occur as projected or not at all.

NEWS RELEASE

March / April 2010



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

Dear Colleagues

Our [web site](#) continues to evolve, most recently through the expansion of the [Patients](#) section. We now offer a link to [Heart-Valve-Surgery.com](#), an outstanding web site set up by a former heart valve patient for the benefit of helping other patients prepare for their procedure and recovery. We also present a [fascinating account](#) of how one patient educated himself on the changing landscape of prosthetic valves, and how he ultimately chose his procedure and his physician.

Besides our travels to visit Institutional Investors, we have also started the conference tour, being invited to the [Design of Medical Devices](#) conference in Minneapolis, Minnesota, and presenting papers at the [Society for Heart Valve Disease](#) in New York and at [EuroPCR](#) in Paris, France. We will also be exhibiting at the [AATS](#) meeting in Toronto. I hope to see some of you at these upcoming meetings.

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

Dr. Vesely Invited to Present Valve Technology Review at Design of Medical Devices Conference

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 Villafana, the founder of St.Jude Medical and co-founder of ATS, his second mechanical valve company, and Dr. Robert Levy, a pioneer in understanding prosthetic valve calcification and in developing methods to mitigate it. Dr. Vesely's presentation can be downloaded in PDF format by clicking [here](#).

Dr. Vesely Presents Animal Data at the Society of Heart Valve Disease Conference

April 15, 2010. New York - Dr. Ivan Vesely, the founder of ValveXchange Inc., presented a paper entitled "*A Rapidly Exchangeable Bioprosthetic Valve*" at the Second Annual Joint Scientific Meeting of the Heart Valve Society of America and the Society for Heart Valve Disease. The paper reviewed the company's progress with chronic animal implants, its experience with exchanging the leaflet set after months of implantation, and its new program to develop a completely non-surgical approach to valve implantation and leaflet exchange.

Other News

Upcoming Conferences

ValveXchange Inc. will be attending the 90th Annual Meeting of the [American Association for Thoracic Surgery \(AATS\)](#) being held at the Toronto Convention center on May 1-5. ValveXchange will have a booth (#1427) and will be displaying the latest outcomes of its product development activities. For those planning to attend the AATS, [booth 1427 is located just beside the Generic Thoracic Hybrid OR display on the east side of Exhibit Hall A](#). We look forward to seeing you at the meeting

Dr. Vesely will also represent ValveXchange at the [EuroPCR meeting in Paris](#), France on May 25-28th. Dr. Vesely's presentation, entitled "*A Transapically Implantable and Exchangeable Bioprosthetic Valve*", will be presented on Wednesday, May 26th, at 17:33 (5:33 PM) in room 243.

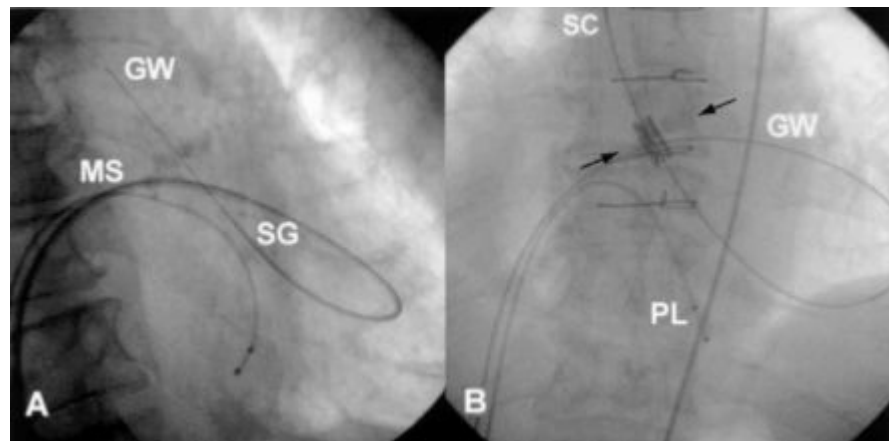
Reality Check

The High Road vs. The Low Road

I have recently been invited to write a review paper about the current state of heart valve technologies for the Journal of Heart Valve Disease. Given what has happened over the past 7 years in the prosthetic valve field, the paper focuses primarily on the design features of transcatheter valves, their clinical and theoretical performance, and how that compares with current and emerging surgical valve technologies.

As I started digging through the literature, a startling outcome emerged with regard to the meaning of "Transcatheter" or "Percutaneous" - the usage of these words has become quite distorted over the past few years. The traditional definition of [percutaneous pertains to any medical procedure where access to inner organs or other tissue is done via needle-puncture of the skin](#). Specifically, the technique involves placing a needle through the skin and into a blood vessel, such as an artery or vein, until bleedback is achieved. This is followed by introduction of a flexible "introducer guide wire" to define the pathway through the skin and into the passageway or "lumen" of the blood vessel. The needle is then exchanged for an "introducer sheath" which is a small tube that is advanced over the introducer guide wire and into the blood vessel. The introducer guide wire is removed, and exchanged for a catheter or other medical device to be used to delivering medication or implantation of a medical implant such as a filter or a stent into the blood vessel (*taken from Wikipedia*).

Indeed, in the original trials by [Cribier](#), the transcatheter valve was delivered via the antegrade approach - through a femoral vein, into the right atrium, through a septal puncture into the left atrium, down into the ventricle and back up into the aortic root (see image below - Note the complex looping of the delivery catheter).



However, the antegrade approach was much too technically challenging for all but the most expert interventionalist, and was quickly supplanted by the retrograde approach through which the femoral artery offered a more direct path to the aortic root. Interestingly, an even straighter path, the transapical approach, is becoming increasingly popular. Indeed, the latest data from a [multi-center clinical trial](#) reports that over 50% of the patients had to be treated with the transapical rather than the transfemoral approach. This occurred because of calcification and tortuosity of the aorto-iliofemoral anatomy that prevented the safe passage of the valve and delivery catheter through the vasculature. Indeed, [many physicians familiar with TAVI](#) now prefer the transapical approach because it avoids the dangers of liberating atheroma from the vasculature and has much lower incidence of Major Adverse Cardiovascular Events (MACE), compared to the transfemoral approach.

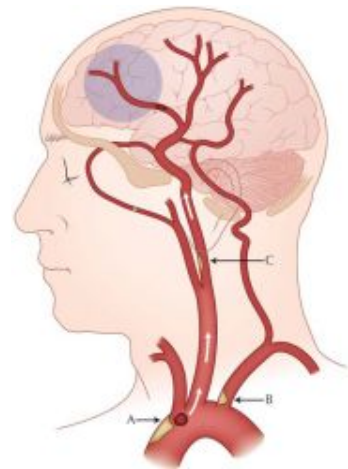
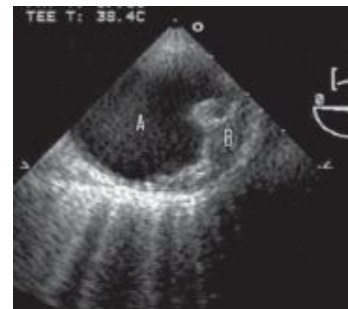
What has been promoted as a non-invasive venous approach (the low road) has thus shifted first to the arterial approach and then to a transapical approach (the high road). Initially, passing devices to the heart through the arterial system was considered more invasive than going through the venous system, because it involves femoral artery incision and subsequent closure of the high pressure femoral artery. [Vascular complications occurred a third of the time](#), often requiring surgical repair. Similarly, a transapical approach was considered more invasive than the transfemoral approach because it involves an incision in the chest wall and exposure of the heart muscle itself. Thus, each of these procedures requires more surgical expertise and greater involvement of the surgeon. What has initially been thought to be an outpatient procedure involving only a venous needle stick and catheterization by interventional cardiologists, has now evolved into an off-pump surgical procedure - less invasive no doubt, but not the routine "catheterization" that was initially envisioned. Opting for the high road (transapical) has been driven primarily by procedural complications and limited access. In the latest publication of a Canadian multi-center study, transfemoral was attempted first, and when that failed the transapical techniques was attempted. That [occurred in over 50% of the cases](#). For highly symptomatic patients with many co-morbidities, the "more invasive" transapical approach appears to be preferable.

TAVI has been in the hands of physicians for a good 5 years and experience with the technology has improved. Centers expert in the procedure report better and better outcomes, particularly with procedural mortality and MACE. For example, when applied to particularly [high-risk patients with Logistic EuroSCORE of 30%, the 30-day mortality was only 8%](#). This is pretty well on par with the operative mortality predicted by the STS score. For example, in a large trial of severely symptomatic patients, [the 30-day mortality after TAVI was 10.4%](#) - this for patients with a 9.8% predicted surgical mortality according to their STS score. Since the STS score is based on the aggregate average of the operative outcomes of nearly 800 participants and over 3 million patient records in the STS registry, TAVI in the hands of the best interventionalists is thus no better than the average STS surgeon. One could argue that had these patients been seen by an above-average surgeon that frequently operates on elderly, frail patients, they would have had better operative and 30-day

mortality. Today's transcatheter valve technology, even in the hands of the most experienced interventionalist, still cannot match the clinical outcomes of the "average surgeon", even for the so-called inoperable patient.

With surgery still looking better than TAVI for even the high risk patients, proponents of TAVI are now saying that [TAVI should move to the younger, healthier patient, as they tend to do better after TAVI than the older, sicker patients](#). In [last month's Reality Check](#), I commented that this would be inadvisable because it would promote the use of inferior, lower-durability valves in patients who would otherwise be candidates for the proven, more durable surgical valves. This would expose patients to earlier re-do procedures for failed prosthetic valves - reversing the 40-year trend in the prosthetic valve field. This month, I will continue that argument with the issue of procedural strokes.

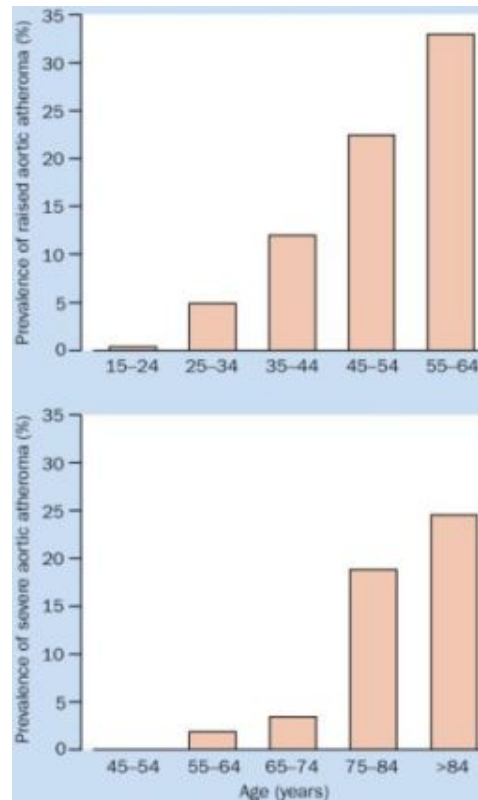
Major Adverse Cardiovascular Events (MACE) are now [8.9%](#) and [3.6%](#) when done in centers of excellence. The likely mechanism is the liberation of aortic arch atheroma. The echo image at right, taken from [Gottsegen et al.](#) shows the lumen of the aorta (A) and a large protruding aortic plaque (B). The diagram of the vasculature below taken from [Sen](#), shows the mechanism by which plaque upstream from cerebral arteries can cause strokes if dislodged by catheter intervention. Indeed, a number of studies have implicated aortic arch atheroma as the mechanism that gives rise to strokes in patients undergoing catheterizations - [the odds ratio for stroke in patients with mobile atheroma is 12](#). Patients with atheroma are therefore 12 times more likely to get a stroke when undergoing catheterizations than patients without atheroma. How prevalent then, is atheroma in the average patient? More specifically, if TAVI were to migrate down to the younger, operable patient with isolated aortic valve stenosis, what is the chance that those patients will have atheroma in the aortic arch that will lead to a significant stroke rate during TAVI?



In a huge study involving autopsies on 2700 people aged 10-64 that died of violence or natural causes, [Strong et al.](#) found raised atherosclerotic lesions in 22% of those aged 45-54 and 33% in those aged 55-64 (see bar graph at right). Atheroma is thus quite common in the healthy population. Interestingly, in a follow-up study comparing American and Asian patients, [patients from New Orleans have three times as much atheroma in their aortic arch than patients from Tokyo](#).

The presence of aortic [atheroma on its own is not a predictor of future strokes](#). Having the disease itself thus does not destine one to eventually get a stroke. The atheroma is likely stable under normal hemodynamic flow - this is probably why so many people live with it. The mechanism by which TAVI patients are at such high risk for stroke is the mechanical manipulation of catheters within the arch that then dislodges the atheroma.

The high incidence of MACE in so-called "inoperable" patients that undergo TAVI is thus likely to remain significant if TAVI were to migrate down to the younger, operable patient. The patients may survive the procedure in greater numbers, live longer because they are healthier, as [noted before](#), but with 30% of all patients aged 55-64 with aortic arch atheroma, the risk of MACE after TAVI is likely to remain significant. Delivery of a valve through the groin (the low road), is likely going to continue to be riskier than delivering the same valve through the apex (the high road), even in the younger, healthier patient. This is why so many physicians now like the approach.



The High Road / Low Road analogy is not just of access, but also one of judgment. Just a week ago, I had a rather unpleasant discussion with an interventional cardiologist. After explaining to him all the current durability deficiencies of transcatheter valves relative to surgical valves, and the demonstrated MACE advantages using a transapical approach versus a transfemoral approach, he finally conceded that *"Current generation transcatheter valves are not going to last more than about 5-7 years"* and that a transapical delivery would lead to better outcomes. However, he finally said *"I'm just not comfortable with the apical approach - it needs a surgeon to close. I'd rather put a transfemoral valve in myself"*.

What is clearly missing here is an objective analysis of what is best for the patient, not what a given physician is *"comfortable with"*. In a very eloquently written [Editorial on the topic of TAVI](#), noted cardiologist and scientist, Blase Carabello, writes:



"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?"

He then continues with an analogy of how cancer patients are treated. A decision of exactly how patients are treated is made by a board of medical, radiation and surgical oncologists that present and review all current data of how patients with similar disease are treated. A group decision is then made regarding the course of best action for the patient in question.

That approach, apparently does not always take place routinely in heart valve therapy. Dr. Friedrich Mohr of Leipzig, a noted expert in all forms of minimally invasive valve surgery and a pioneer in the transcatheter valve field commented at the latest meeting of the Society for Heart Valve Disease that while surgeons can operate on practically all patients with a wide range of co-morbidities with good clinical success, the cardiologists simply *"do not send them."*



That is the sad reality in a system where cardiologists and surgeons compete for patients. While the practice may be different in many countries with different healthcare management systems, it continues to flourish here in the US. Ultimately, it is the patient that may be left with less-than-optimal therapy. Patients clearly cannot make truly "informed consent" decisions in a field with such overwhelming complexity of data - they typically listen to the physician that they see first and accept whatever mode of therapy that physician recommends.

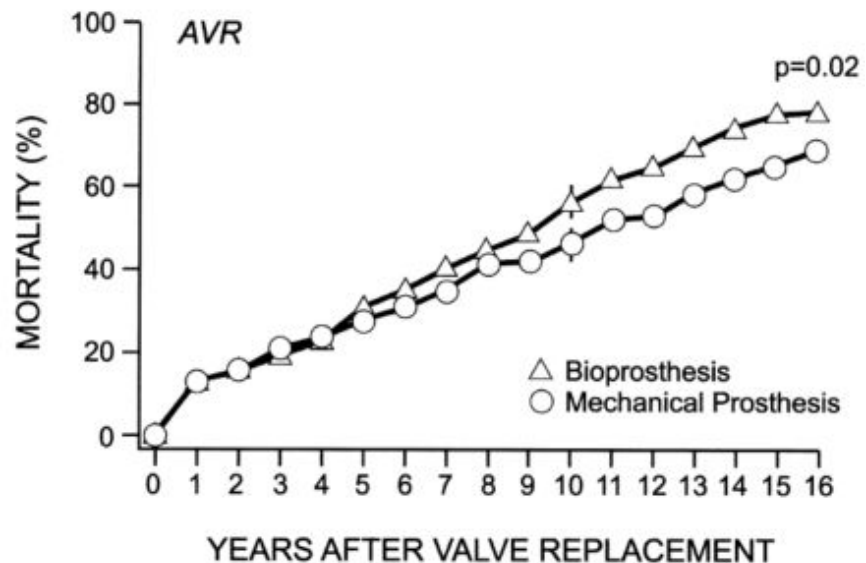
Interestingly, with the prevalence of the web, patients are gradually becoming more informed about the range of therapies available to them. More importantly, they are educating themselves about which physicians are expert in the range of surgical procedures they will experience. One such patient that I have recently met is Adam Pick, a young individual that underwent the Ross procedure in 2005. Adam did a lot of personal research as to which physician to choose prior to his surgery. He then developed an outstanding [web site for patient reference](#), as well as a [fascinating book](#) about his own surgical experience.



Of course, Adam Pick was not a candidate for TAVI. Mel Heller, however, was. Dr. Mel Heller is a retired physician and 87 years old. When faced with the prospect of needing aortic valve surgery, he took matters into his own hands and studied up on the subject. He was initially referred to a center that participates in the Edwards PARTNER trial for a transcatheter delivery of the Sapien® valve. There he was told that he would be a good candidate for this TAVI. After reviewing the clinical data on the web, he ultimately chose to undergo conventional surgery and have a high-quality surgical valve implanted instead. I got to know him through an interesting trail of personal colleagues and helped him in a small way by referring him to a physician colleague, Dr. Michael Banbury (pictured at right), who ultimately did his surgery. Dr. Heller's account of how he came to his decision is a fascinating one, and is [reproduced on our web site](#).



In a perfect world, the interests of valve manufacturers, cardiologists and surgeons would be aligned. Patients would get the therapy that is best for them. Before the advent of TAVI, we were close to that - we had surgical valves split between mechanical and bioprosthetic. Patients were managed in the most optimal way. Long-term mortality between the groups was nearly identical. The graph shown below is taken from the work of [Rahimtoola](#), a known expert in prosthetic valve epidemiology.



These data show that that the late complication rates between patients receiving mechanical and bioprosthetic valves are nearly identical. When all the complications resulting from the use of mechanical valves and Coumadin® are compared to the complications associated with the use of tissue valves and the incidence of reoperations, they are essentially equivalent. This means that, in hind-sight, patients have received optimal treatment.

With the advent of TAVI, we have the opportunity to go one step further, to combine the long-term successes of surgical valves with the least invasiveness of transcatheter and minimally invasive technologies - to reduce the slope of that curve even further. That will involve restraint and careful attention to data and historical precedents. In the words of Dr. Blase Carabello taken from his [editorial](#):

"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."

Summary:

The company [Google has an interesting informal company motto](#) - "*Don't be evil*". While somewhat tongue-in-cheek, it has driven some recent company decisions. "*Do no harm*" is one of the [principal precepts of medical ethics](#) that all medical students are taught in medical school. We, at ValveXchange, intend to uphold similar standards of corporate ethics when it comes to product development. Our Vitality™ surgically implantable, transapically exchangeable valve is designed to bring a Coumadin®-free lifestyle to patients of all ages. That valve promises to lower the slope of [Rahimtoola's](#) curve considerably. Our Vanguard™ transapically implantable, exchangeable valve is an evolutionary approach to valve therapy - not a radical departure. It builds upon the 40+ year history of prosthetic valve technologies and reduces the invasiveness of implant without sacrificing patient safety. That is our founding principal - **The future of heart valve therapy; without compromise.** At ValveXchange, we're taking the high road!

Sincerely,

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

Recent News Releases

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.](#)



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