

**In This Issue**

[Press Release](#)

[Technology Report](#)

[Reality Check](#)

[Previous News Releases](#)

**About Us**

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

**Join Our List**

[Join Our Mailing List!](#)



**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**

May / June 2010



**From the Desk of Ivan Vesely, Ph.D.**

Dear Colleagues

May and June witnessed another busy travel schedule, with booths and presentations at the [AATS meeting in Toronto](#), and the [EuroPCR meeting in Paris, France](#). At the EuroPCR meeting, we also participated in the Innovation Showcase with an oral presentation to a full-house audience.

Having demonstrated the exchangeability of the surgically-implantable Vitality™, we have moved towards the transapically implantable Vanguard™ docking station. This is proceeding in concert with a precision plastic mock-up model of an anatomically accurate sheep heart derived from spiral CT imaging. The model will be used for pre-operative planning to maximize the success of the implant procedure testing and tool refinement.

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

### Lars Svensson joins VXi Medical Advisory Board

**June, 2010. Denver** - ValveXchange Inc. is pleased to announce that Lars G. Svensson, MD, PhD, has joined the VXi Medical Advisory Board. Dr. Svensson obtained his medical degree in 1978, a MSc in 1983 and a PhD in 1986 from the University of Witwatersrand, Johannesburg, South Africa. His cardiology, general and vascular surgery training was at the Johannesburg Hospital, followed by cardiovascular surgery training at The Cleveland Clinic Foundation, Cleveland, Ohio, and Baylor College of Medicine in Houston Texas, including cardiothoracic surgery residency. He is board certified in general, vascular, and cardiothoracic surgery. He was Chief of Cardiovascular Surgery at Houston VAMC and worked with Drs. DeBakey and Crawford at Baylor College of Medicine. He was Assistant Professor of Surgery at Baylor College of Medicine, and then Professor of Cardiothoracic Surgery at Tufts, and Instructor at Harvard Medical School while working at the Lahey Clinic in Boston. In 2005 he was made King James IV Professor of Surgery of The Royal College of Surgeons of Edinburgh. He is on numerous committees, including the Society of Thoracic Surgery / American Association for Thoracic Surgery Government Relations Committee, STS Endovascular Task Force, AHA/ACC/AATS/STS Guidelines Committee for Aortic Disease, NHLBI Committee on Aortic Disease Research and Marfan Syndrome, Chairs the STS / AATS Endovascular Expert Opinion Committee, and Cleveland Clinic Surgery Committee. He is on the editorial board of several journals including the Journal for Thoracic and Cardiovascular Surgery and past Associate Editor of Annals of Thoracic Surgery. He is Director for the Aortic Surgery Center and Marfan Syndrome and Connective Tissue Disorder Clinic at The Cleveland Clinic Foundation. His interests are minimally invasive valve surgery, percutaneous cardiovascular surgery, and brain and spinal cord protection during cardiovascular surgery. His hobbies are photography and sailing.



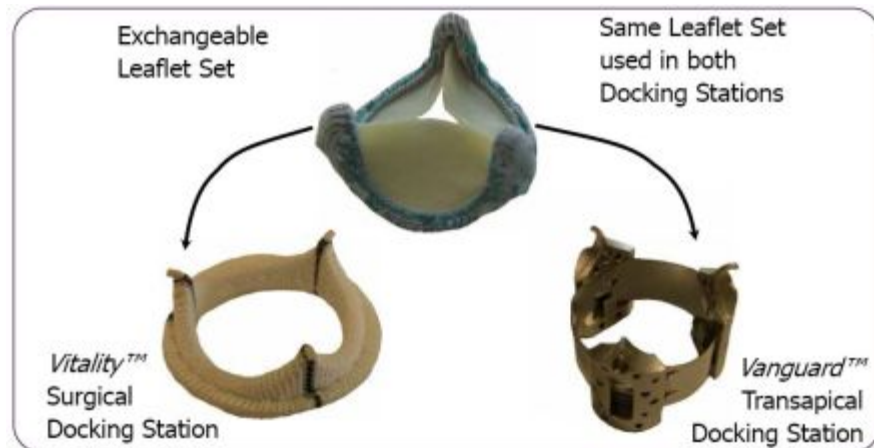
### Dr. Vesely Presents Recent Animal Data at EuroPCR

**June 1, 2010. Paris, France** - Dr. Ivan Vesely, the founder of ValveXchange Inc., delivered a progress report on company activities in an oral presentation entitled "A Rapidly Exchangeable Bioprosthetic Valve", at the 2010 EuroPCR meeting in Paris, France. This presentation took place in the context of an Innovation Showcase in which 7 other emerging company representatives presented their technologies to a standing room-only audience. Dr. Vesely's presentation can be downloaded in PDF format by clicking [here](#).

## Technology Report

### The Transapically Implantable Vanguard™ Docking Station

Having demonstrated the exchangeability of the Vitality™ surgically implantable docking station in large animal testing, attention and development efforts have now turned to the Vanguard™ transapically implantable docking station. The transapically-implantable Vanguard™ has a number of important advantages over existing transcatheter valve designs.



First of all, it subscribes to the "Three Tenets of Good Valve Design" that have been presented in this forum many times before. These being: (i) flexible stent posts, (ii) absolute circularity, and (iii) perfect 120° symmetry. These design principles are adhered-to in the transapically-implantable Vanguard™ by using the same leaflet set as in the surgically-implantable Vitality™. The expanding metal band of the Vanguard™ docking station also has far greater hoop stiffness than current generation transcatheter valves and can thus be deployed into a truly round shape and to a known, fixed diameter. The leaflet set is fabricated to fit onto a fixed diameter docking station and is thus designed to function properly and with full durability in this deployed configuration.

Secondly, the leaflet set is not crushed inside of the metal frame during collapse as are most other transcatheter valves, and is thus not potentially damaged during "crimping" of the docking station. It is positioned distal to the docking station during delivery and "snapped in place" after the docking station is fully expanded. This in-situ assembly also allows for improved packaging, making the Vanguard™ feasible for not only its initial transapical delivery approach, but also for eventual transfemoral delivery

The most important feature of the Vanguard™ is that which will enable MIS, off-pump tissue valve implantation to penetrate into the younger patient population - its adherence to good valve design principles and thus its long-term durability, combined with its leaflet exchangeability. Indeed, long-term durability by way of perfect circularity is no longer being

preached only by us at ValveXchange, but has become a point of mainstream discussion at conferences, like at EuroPCR. More importantly, well-recognized authorities on transcatheter valve authorities, like Dr. Marty Leon are openly questioning the issue of non-circularity with current-generation transcatheter valves, citing the [Zegdi references](#) that we have presented here well over a year ago. Recently, Dr. Leon was the host of a fascinating interview with valve experts at the EuroPCR meeting which is available for review on TheHeart.org [web site](#). In that interview, three expert panelists, Dr. Alain Cribier (recognized as the inventor of TAVI), Dr. Neil Moats (Director of the TAVI program at Royal Brompton Hospital), and Dr. Carlos Ruiz (noted authority on TAVI from Lenox Hill Hospital) spoke about the future issues of transcatheter valves.



Dr. Neil Moats    Dr. Alain Cribier    Dr. Carlos Ruiz    Dr. Marty Leon

Dr. Leon was particularly concerned about durability and posed the question of how do we move TAVI from the extremely high-risk patients to other groups in a truly safe fashion.

Dr. Moats specifically commented on the non-circularity of current generation valves when deployed, and how that will affect their long-term durability when applied to lower risk patients. He quoted the "*lessons learned with stentless valves and the effects that non-circularity has on long-term durability*". Interestingly, Dr. Moats stated that the truly high-risk patients continue to do badly after aortic valve replacement, suggesting that TAVI may not be an effective solution for them. The next wave of patients that might benefit from TAVI are the lower-risk 80+ year-old patients with co-morbidities. These patients should receive TAVI only by way of large randomized clinical trials so that clear benefit of TAVI in these patients is demonstrated, ideally through "*10 year data on their durability*." Dr. Moats also mentioned the potential risks involved in crimping valves inside the frame in order to get very "*low-profile*" devices - valves that can be delivered through very small introducers - and the impact on their durability.

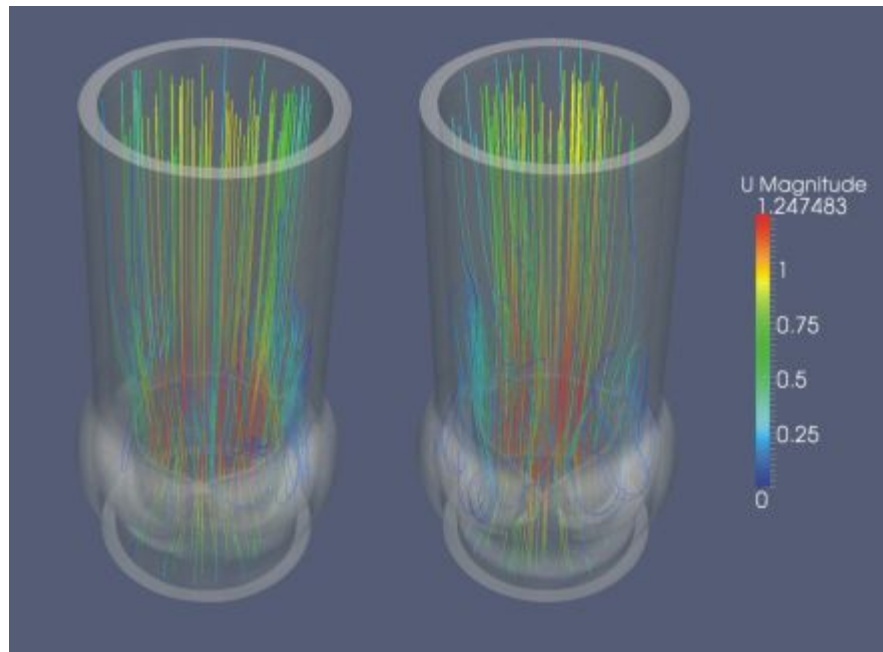
With regard to the introducer, Dr. Cribier commented that "*size is not important - the most important issue is the ability to deliver a good valve*". He further added that "*transcatheter valves should have all the characteristics of surgical valves*", commenting particularly on the long-term durability and the circularity of the deployed device. With regard to moving TAVI to the younger patient, his estimates were that TAVI would encounter "*70% bicuspid valve if used in patients younger than 70 or 65*".

years of age". He said it would be "difficult to imagine" how TAVI would work in these patients.

With a valve platform that ensures perfect circularity when deployed, and thus durability equivalent to that of surgical valves, ValveXchange is well positioned to lead the "second wave" of transcatheter valves into the younger, operable patient population.

### **Computational Fluid Dynamics Modeling reveals flow through VXi Vitality**

In ongoing efforts to demonstrate the quality of our products in comparison to industry standard surgical valves, we have recently completed a Computational Fluid Dynamics (CFD) study of the VXi Vitality™ valve and the Edwards Perimount™. We obtained 23 mm versions of both valves and subjected them to micro CT scanning with the leaflets held in an open position. The 3D CT images were then converted to surface rendered 3-D models and placed into a computational "volume" of fluid and solid that mimics the aortic root. Fluid motion within the models was simulated to mimic systole and any differences in flow through the two valves noted. Preliminary data thus far indicate no significant differences between the two valves. In the image below, the Edwards Perimount valve is shown on the left, and the ValveXchange Vitality is on the right.

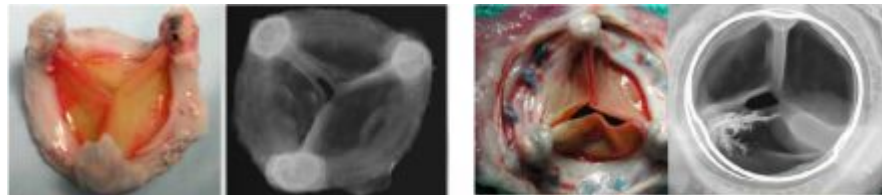


This work is being done in the [laboratory of Dr. Daniel Einstein](#), a Scientist in the Pacific Northwest National Laboratories, a division of Battelle, under a contract from ValveXchange. Dr. Einstein is perhaps the most accomplished scientist in the field of solid and fluid modeling of heart valve function, having worked on both aortic and mitral valves, and in the fields of solid and fluid dynamics and their interactions.

### **Long-term sheep implants consistently show excellent calcification resistance**

The adolescent sheep model is prescribed by the FDA as a pre-clinical testing ground for bioprosthetic heart valves. Because the growing sheep calcifies bioprosthetic valve tissues quickly, most valves develop some form of leaflet mineralization after 5 months of implant. Five months is the maximum implant period prescribed by the FDA, as valves typically do not last much more beyond that in the sheep. With an exchangeable leaflet valve, however, we have been breaking unofficial records of valve implant duration in the aortic position. In two separate cases, we implanted the VXi Vitality™ into a sheep and exchanged the leaflet set 3 months later. The sheep recovered well and continued to thrive. We then decided to do another leaflet exchange 5 months later. By then, the sheep had the original docking station implanted for 8 months, and went through 2 leaflet sets. We thus have a good number of Vitality™ leaflet sets that have survived in the sheep for 3 months and 5 months. None of them have torn or exhibited other signs of degeneration or calcification, and all exhibited good leaflet coaptation at explant. In a comparison study, we implanted 3 Edwards Perimount™ valves into the same sheep model and explanted the valves at 5 months. One of the valves had no visible mineralization, and two had moderate calcification and some leaflet distortion. None of the VXi valves had any mineralization when subjected for X-ray imaging.

In the images below, a Vitality™ leaflet set explanted at 5 months is shown at left, both as an optical image and as an X-ray micrograph. Similar views are shown for the Edwards Perimount™ at right. Note the mineralization of the Edwards valve that is visible in the X-ray micrograph, corresponding to the slight leaflet deformation visible in the optical image. We are thus very happy with the performance of our valves in the sheep model and early results suggest that the VXi Vitality™ is at least as good as the Edwards Perimount™ in terms of mineralization resistance, if not better.



---

## Reality Check

### Back to the Future:

With all the advances in delivery methods and component packaging that ValveXchange has been working on over past year, it is useful to step back and reflect on the therapeutic basis upon which ValveXchange, Inc. was founded.

Historically, patients that need artificial heart valves can receive either bioprostheses made from animal tissues, or mechanical valves made from synthetic materials. Bioprostheses have few complications, allow a full and active lifestyle and are considered the ideal valve for most patients. However, they wear out in about 15 years - sooner in younger patients, at which time another open-heart surgery is required. Mechanical valves, on the other hand, will last the patient's lifetime but come with anticoagulation-related complications, such as strokes or break-through bleeding, and are usually used if the patient is too young to receive a bioprosthesis. Prosthetic valves are therefore meant to be implanted once, and should last the life of the patient. Indeed, the ACC-recommended cut-off age for the use of tissue valves is 65 years. If a patient is too young and is expected to outlive a tissue valve, they receive a mechanical valve. Older patients have therefore enjoyed the benefits of bioprosthetic valves whereas younger patients have had to manage with the lower quality of life associated with mechanical valves. The use of tissue valves in younger patients, however, has [doubled over the past decade](#). Today, younger patients tend to choose tissue valves over mechanical valves, even if they run the risk of outliving their implant and having to undergo one or more subsequent open-heart surgeries at an advanced age. Although part of this is because surgery has become relatively safe ([1% for asymptomatic patients](#)), the main reason is the refusal to put up with Coumadin (the registered trade name of the anticoagulant drug Warfarin) and its attendant lifestyle compromises. Because of this trend towards using tissue valves in younger patients, the number of reoperations for bioprosthetic valve failure has been rising. Recent data reports [freedom from reoperation](#) at 10, 15 and 20 years being 76%, 61% and 59%. In young adults, [reoperation for bioprosthetic valve degeneration is 55% at 15 years](#).

With reoperation now being considered an acceptable alternative to Coumadin and mechanical valves, we have strived to make reoperation faster, safer and less invasive. Although the first reoperation can be almost as safe as the initial surgery ([usually 2%](#)) it is highly dependent upon the experience of the physician. Technologies that minimize complications during valve replacement procedures and maximize the time between re-interventions, are thus desirable. To that end, we have been developing a rapidly exchangeable valve that not only minimizes the magnitude of the intervention, but also maximizes the time between interventions. We thus have a highly durable bioprosthetic valve, with performance on par with the industry leaders like the Edwards Perimount™.

The importance of a long-lived tissue valve, regardless of how it is delivered, has finally made it into collective consciousness of the proponents of TAVI, as evident by the sober discussions at [EuroPCR](#), highlighted by the [Marty Leon interviews noted above](#). The importance of using a tissue valve, instead of a mechanical valve has been brought to light recently by way of a [fascinating article in the New York Times](#). This article reports that *"One-third to one-half of all patients do not take medication as prescribed, and up to one-quarter never fill prescriptions at all... Such lapses fuel more than \$100 billion dollars in health costs annually because those patients often get sicker."* The article continues with a report on how a program in Philadelphia has been paying patients to take warfarin (Coumadin). In one example, a patient with lupus reported that she *"would forget to take it"* and feel *"like she couldn't breathe" or she would "take two in one day" and develop bruises from uncontrolled internal bleeding.* The Philadelphia program thus instituted a lottery in which patients could win up to \$100 per day for staying on Coumadin. This incentive apparently completely turned this non-compliant patient around allowing her to pocket \$300 over 6 months. *"You got something for taking it"* reported the patient, adding *"I was taking it regularly, I was doing so good"*. Another patient on warfarin commented that the lottery project was *"like a game. I didn't miss one time.. and.. couldn't wait to get to the machine"* to see if he had won money for taking warfarin the previous day. The project's directors at the University of Pennsylvania Medical School said they *"chose warfarin because it can be very dangerous if not taken faithfully."*

Now clearly, this program has many detractors that argue that *"Once you start paying people to take medication, when do you stop paying them?"* But the reality of patient non-compliance has prompted Aetna, the insurer, to support the Philadelphia experiment and consider expanding such programs - a cost reduction measure no doubt. Apparently the \$90-a-month average payment to the patient will quickly *"pay for itself if it prevents two emergency clinic visits."* *If it prevents a "cerebral hemorrhage or a major clot, we save tens of thousands of dollars."*

The [New York Times article](#) is timely in that it supports an internal study at ValveXchange with regard to quantifying the ongoing costs of Coumadin-related complications in patients with mechanical valves. By way of this study, we found that once costs of all the complications of Coumadin were tabulated, even two leaflet exchanges over 30 years appear to be far cheaper than being on Coumadin, not even considering the patient's significant quality of life improvement. Our numbers show that if you add up all the complications that lead to Emergency Department visits, multiply their costs by the probability of their occurrence over 30 years, the total costs are as much as \$155,760 per patient with a mechanical valve.

With cost-effective healthcare so much in the public view of recent months, the *"tissue valve for patients of all ages"* approach makes more sense than ever before. With HMO's and insurance providers beginning to consider the long-term cost repercussions of Coumadin patient non-compliance, and actually paying their clients to take their Coumadin to avoid Emergency Department visits, recommending a tissue valve for their

patients may not only be the best choice from a health and lifestyle point of view, but also the best with regard to cost management.

Here is how we did our Coumadin costing study:

There are typically two main sets of costs associated with any clinical intervention at a hospital. Those include facility costs for the procedure, many times covered by a [DRG \(Diagnosis Related Group\)](#) reimbursement, and other costs paid for by other means, such as [CPT \(Current Procedure Terminology\)](#) reimbursements for physician specialty services. We looked at these and other sources to determine the average costs for treatment of complications reported in the literature for Coumadin patients. Such charges vary throughout the country, so we selected the costs in our area, Denver, Colorado as a baseline. Denver tends to be a moderate cost area, neither the least nor most costly. For example, in Colorado, a practitioner will receive an average of \$256 under the CPT code for Cardiopulmonary Resuscitation, while the total cost for coronary angiography averages \$11,383.

To determine the medical interventions associated with long-term use of Coumadin, we researched published literature that identified the major problems that a patient on Coumadin with a mechanical valve could have and tabulated them on a large spreadsheet. Managing Coumadin "properly" involves a series of steps. Taking the medication as prescribed is only one part of a more complex problem. Variations in patient factors including diet and other drugs can affect the patient's sensitivity to Coumadin and therefore the amount to be taken. Frequent blood monitoring is required to adjust for these factors. If a patient is not managing Coumadin properly or their condition has changed and the result is under-medication, the primary risks are from Thromboembolism, which could lead to:

- (i) Myocardial Infarction (MI)
- (ii) Pulmonary Embolism (PE)
- (iii) Cerebrovascular Accident (CVA)
- (iv) Transient Ischemic Attack (TIA)
- (v) Renal Infarct, or
- (vi) Hepatic Infarct

If a patient is not managing Coumadin properly or their condition has changed and the result is overmedication, the primary risks are from uncontrolled bleeding, and the patient could experience:

- (i) Intracranial Hemorrhage (ICH)
- (ii) Subarachnoid Hemorrhage (SAH), or
- (iii) Gastrointestinal Bleeding

Such patient conditions have also been correlated with traumatic falls with a variety of injuries resulting, including hip fracture.

The above events are typically reimbursed under the DRG groups, with costs ranging from \$15,166 for a Renal Infarct, to \$83,879 for an uncontrolled GI bleed.

Once a patient is diagnosed with a particular condition (DRG Code), an uncontrolled GI bleed for example, then a series of interventions are done to treat the condition. These treatments are then associated with the corresponding cost, as shown in the table below.

Abdominal GI Bleed, Probability 1.7%/year						
Avg DRG Amount	Treatment	CPT Code/Source	Unit Cost	Multiplier	Treatment Cost	Total non-DRG
\$83,879	EMS Arrival via Ambulance		\$388.26	1	388.26	\$9,090
	IV Fluids	90760	\$204	1	204	
	CP Resuscitation	92950	\$256	1	256	
	ECG	93000	\$30	1	29.85	
	ER Admit	99285	\$195.88	1	195.88	
	CBC		\$204	1	204	
	PTT w/ INR		\$73	1	73	
	Liver Enzyme Panel		\$87	1	87	
	Cross Match for 2 units of RBC		\$42	1	42	
	Placement of NG Tube	43752	\$43.74	1	43.74	
	Blood Transfusion		\$1,585	1	1585	
	Dr Critical Care 1 hour	99291	\$115.84	1	115.84	
	Dr Add 30 min CC	99292	\$197.01	1	197.01	
	ECG Monitoring/Report/ DR Review	93235	\$133.58	1	133.58	
	Initial Hospital Care Per Day	99221	\$98.11	1	98.11	
	Subsequent Hospital Care Per Day	99231	\$133.97	4	535.88	
	Upper GI Endoscopic Exam	43234	\$125.30	1	125.30	
	Upper GI Endoscopic Diagnosis	43235	\$147.97	1	147.97	
	Endoscopic Treatment:Control Bleed	43255	\$299.07	1	299.07	
	IV Proton Inhibitors Pump		\$100.00	1	100	
	Upper GI Endoscopy w/ Stent	43256	\$290.49	1	290.49	
	Intrarterial Embolization	37210	\$613.15	1	613.15	
	Artery Rupture & Repair	35122	\$2,185.28	1	2185.28	
	Transvenous Intrahepatic portosyst	36145	\$110.72	1	110.72	
	Nuclear Bleeding Scan	78278	\$354.52	1	354.52	
	Angiography	74175	\$578.04	1	578.04	
	Colonoscopy	57452	\$96.14	1	96.14	

A hospital that treats a patient diagnosed with an MI thus bills \$83,879 per the DRG, and individual bills for all the associated treatments may add up to an additional \$9,090.

While the costs are clearly very high, the probability of these events happening is low. The high costs of these treatments thus need to be multiplied by their yearly probability of occurrence. We thus searched the literature to identify the likely probability of a patient with a mechanical valve experiencing any one of the events listed above associated with under- or over-medication of Coumadin. For example, if the patient is under-medicated, the probability of an uncontrolled GI bleed is [1.7% per year](#). Multiplying the cost of treating the GI bleed by its probability of occurrence (\$92,969 x 0.017) yields an annual probable cost per patient of \$1,580. Over 30 years, the probability of this complication occurring is 51% (30 x 0.017), and the likely costs of treating the patient \$47,414. Clearly, the probability of occurrence of any of these complications will have a significant impact on the cumulative costs. Our analysis used probabilities of occurrence of warfarin complications from peer reviewed publications. These preliminary result indicate that over 30 years, the probable costs for treating Coumadin-related complications will be \$65,550, if the patient is undermedicated, and \$155,760, if the patient is overmedicated.

Market studies project that an average of 27,000 mechanical valves will be implanted in the US each year through 2015. This implies a 30-year cost burden on our society of \$1.8 - \$4.2 Billion for each year we maintain this

level of mechanical valve implants. Even if these numbers were halved, they would represent a huge potential financial burden. It is thus no wonder that some insurance carriers are considering paying patients in cash, just to take their daily pills. Although preliminary, our study has given us enough cause for concern regarding the future cost burdens associated with mechanical valves and Coumadin therapy. We are now working with noted clinicians to refine this study further, both for the probability of event occurrence and for the actual costs of treating the patient.

With regard to paying patients to take their daily pill, that is still just a small piece of the puzzle. Patients on anticoagulation therapy must also follow dietary restrictions, particularly [monitoring vitamin K intake](#), otherwise their [INR](#) will fluctuate, even if they take their Coumadin daily. Even in the best of cases where Coumadin is well monitored, chronic use of Coumadin has been shown to increase the rate of mineralization of other valves and vascular tissues by a factor of two ([ref1,ref2](#)).

Putting all patients on good quality tissue valves that address reoperation issues, like the ValveXchange Vitality™, seems like the best way to get around these complications.

I expect that supporters of mechanical valves will argue that the above is a blatantly self-promoting statement. They may argue that some day we will have better anticoagulation drugs that will herald the comeback of the mechanical valve. That appears to be a long-shot. In a recent article in the [Journal of Cardiovascular Pharmacology and Therapeutics, entitled "Will Warfarin Ever Be Replaced?"](#), the authors review published data and clinical profiles of the most promising new oral anticoagulants in late stage development - edoxaban, rivaroxaban, apixaban and dabigatran.

The primary limitation of Coumadin and other Vitamin K antagonists is that they inhibit multiple vitamin K dependent factors in the coagulation cascade (factors II, VII, IX and X). Coumadin also has a slow onset of action, has multiple drug and food interactions, is subject to genetic variability in its metabolism and requires frequent monitoring of the INR because of a narrow therapeutic window.

The primary advantage of **Dabigatran** is that it is a direct thrombin inhibitor that has a broader therapeutic window. It has been tested in total hip and total knee surgery and approved in Europe and Canada for the prevention of venous thromboembolism. Following good performance in US trials for managing atrial fibrillation (AF), Dabigatran is now being considered for the prevention of stroke and systemic embolism in patients with AF.

**Rivaroxaban** is a direct and reversible inhibitor of Factor Xa. It is also approved for the treatment of venous thromboembolism in Europe and Canada. It is, however, contraindicated in patients with liver and renal disease. US trials are ongoing to consider its use in Acute Coronary Syndrome and Atrial Fibrillation.

**Edoxaban** is another direct inhibitor of Factor Xa with very linear pharmacokinetics across a broad dosage range (10 to 150 mg), and without regard to food intake. It does interact with verapamil, quinidine and

similar drugs to treat heart rhythm disturbances. US trials for thromboembolism and atrial fibrillation are ongoing.

**Apixaban** is also a new Factor Xa inhibitor that is rapidly absorbed. It failed to meet the noninferiority criteria in a recent venous thromboembolism trial randomized against subcutaneous injections of enoxaparin. The drug, however, did show a 38% reduction in deep vein thrombosis in a subsequent trial with different dosages of the competing drugs. It is also being tested for the treatment of acute coronary syndrome and atrial fibrillation.

The primary metabolic differences between the drugs are shown in the table below.

Name Company	Dabigatran Boehringer	Apixaban BMS/Pfizer	Rivaroxaban Bayer/J&J	Edoxaban Daiichi Sankyo
$C_{max}$	2 h	1-3 h	2-4 h	1-2 h
CYP metabolism	None	15%	32%	NR
Bioavailability	7%	66%	80%	> 45%
Transporters	P-gp	P-gp	P-gp/BCRP	NR
Protein binding	35%	87%	>90%	55%
Half-life	12-14 h	8-15 h	9-13 h	8-10 h
Renal elimination	80%	25%	66%	35%
Linear PK	Yes	Yes	No	Yes

NOTE: BCRP = breast cancer resistance protein;  $C_{max}$  = time to maximum concentration; CYP = cytochrome P450; h, hours; NR = not reported; P-gp = P-glycoprotein; PK = pharmacokinetics.

Although all of these drugs show promise in treating venous thrombosis, they are all being scrutinized for liver safety due to the failure of a similar drug, ximelagatran, to get FDA approval because of its serious liver toxicity. Unlike warfarin, none of these new drugs also has a clinically tested reversal agent. Their use in preventing thromboembolism of mechanical valves, where the INR needs to be greater, is largely untested. For the treatment of [atrial fibrillation, the INR is typically set at 2.0-3.0](#), with a target of 2.5. Patients with mechanical valves typically have [INR of 3.0 or greater](#). Experience with the new classes of drugs in venous thrombosis will thus be difficult to translate to their usage in mechanical valves, unless additional clinical trials are initiated.

Experts in the field now suggest that with the good durability of current generation tissue valves, and the prospect of nearly complication-free valve redo's, mechanical valves and Coumadin are on their way out. We hope that their demise can be accelerated by the exchangeable valve technology of VXI.

---

## Summary:

I chose to revisit the original basis for an exchangeable valve primarily because of that surprising New York Times article about HMOs paying their patients to take Coumadin. With all the buzz about transcatheter valves over the past 5 years, the ongoing plight of the younger patient that needs a prosthetic valve has been all but ignored. By recognizing the underlying challenges that patients have in selecting an appropriate heart valve, we have thus returned **back to the future** of heart valve therapy - a tissue valve for patients of all ages.

Sincerely,

Ivan Vesely, Ph.D.  
Founder and Chief Scientific Officer  
ValveXchange Inc.  
[vesely@valveXchange.com](mailto:vesely@valveXchange.com)

---

## Recent News Releases

**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.](#)

