AORTIC STENOSIS TREATMENT AND THE PATH TO POLYMER VALVES

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The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota State University's regulations and meets the accepted standards for the degree of

MASTER OF SCIENCE

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ABSTRACT

All available heart valve medical devices on the market are made from biological tissues. The major drawback of using biological tissue is that it is prone to calcification, which is generally why the intervention was needed in the first place. There is also the limitation of lifetime of the device; because it is a biological material it is more prone to degradation, wear, and tear. This leaves room for improvement of the valve device, to move from a tissue valve to a polymer valve. There has been great promise with preliminary materials studies showing resistant to calcification and an almost doubling lifespan for a valve. However, none of this proposed polymer valves have gone through clinical testing and are in general still being bench-top studied. There is ample room for companies or research groups to explore medical device innovation relating to a polymer leaflet material.

ACKNOWLEDGMENTS

I would like to thank my NDSU advisor Mohi Quadir for supporting me throughout this process. I would also like to thank Steve Laudenbach from Boston Scientific for always supporting my academic endeavors.

DEDICATION

To my mom who set the bar high. My husband who fully supports all my crazy plans. To my son, Max, to never stop learning.

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LIST OF ABBREVIATIONS

CAVD .....Calcified Aortic Valve Disease.

TAVI .....Transcatheter aortic valve implantation.

TAVR.....Transcatheter aortic valve replacement.

SAVR .....Surgical aortic valve replacement.

ESC .....European Society of Cardiology.

CI.....Confidence interval.

HR .....Hazard ratio.

RCT.....Randomized clinical trial.

AS.....Aortic Stenosis.

ISO .....International Organization for Standardization.

NIH.....National Institutes of Health.

HA-LLDPE .....Hyaluronan linear low-density polyethylene.

POSS-PU.....Polyhedral oligomeric silsesquioxane polyurethane.

PPE.....Personal Protective Equipment.

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INTRODUCTION

The heart is the central transit station in charge of pumping and forcing blood to travel throughout the body to either deliver oxygen to tissues and organs, or to collect oxygen from the lungs that will then go on to be delivered to the organs and tissues. Blood flow is powered by the pressure differences made by the four different valves- mitral, tricuspid, aortic and pulmonary– which are responsible for the common sound of a heartbeat, the "lub-dub" sound. Each valve opens and closes an average of 108,000 times a day[1]. Taking into account the average life span of 78 years in the United States, means each valve in our heart performs 3.1 billion movements in a lifetime. With this many movements over a lifetime there is a lot of stress and fatigue that occurs on these valves.

The well-being of the body fully relies on the capability of these valves functioning properly over the course of 3.1 billion movements each. If a valve does not close and seal correctly, then a backwards flow of blood will have an impact on the efficiency of the heart. If the tissues and organs do not receive all the oxygen they need to function, they may begin to operate less efficiently themselves or even begin to deteriorate causing even more downstream harm. A small problem that begins with one valve, can have a cascade effect on potentially every organ. Certainly, affecting the quality of life for a person quite dramatically. For this reason, it is imperative that action be taken to resolve heart valve disease to maintain a high quality of life and to also prevent further organ involvement.

BACKGROUND

From a recent publication in 2022, it was stated that diseases related to the aortic valve account for 61% of all valvular heart disease deaths; with aortic valve disease being well understood as being associated with old age and chronic cardiovascular disease.[2] Aortic stenosis is the most common primary valve lesion that requires surgery and/or transcatheter intervention within Europe and North America.[3] Calcified aortic valve disease, CAVD, affects roughly 0.9% of the US population, with 2.8% of people 75+ years having moderate to severe cases.[4] Figure 1 is a visual representation of calcific stenosis on the aortic valve. The normal valve is able to fully close and seal, while the stenotic valve is unable to mechanically function correctly and leaves gaps in the closure because of the stiff nature of the damaged valve leaflets. Because the diseased valve is unable to fully close, the efficiency of the valve and overall heart is dramatically impacted and results with less oxygen being delivered to the body.

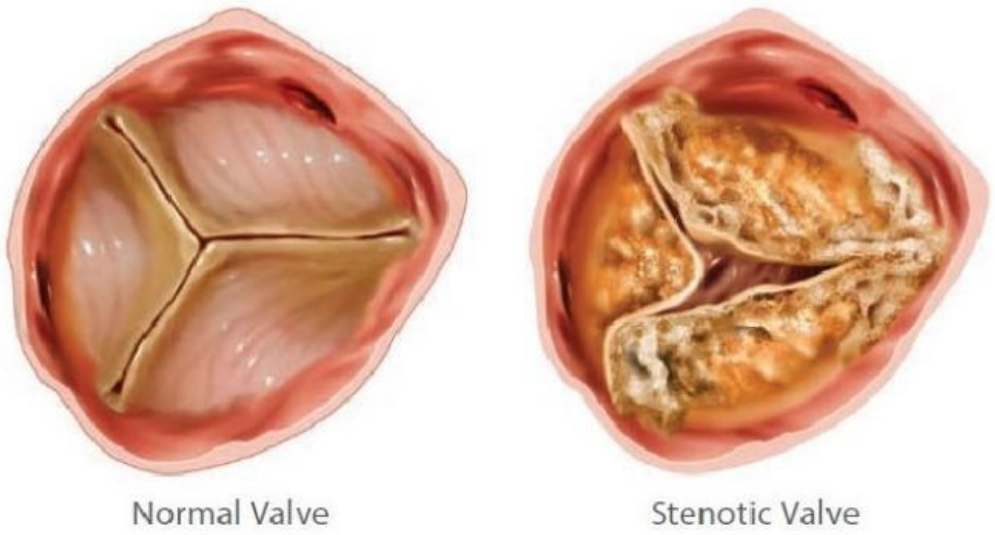

Figure 1. A visual representation of a normal valve and a calcific stenosed valve.[5]

Because the deaths from CAVD outweigh the other valves and stenosis being a high factoring disease state, this paper will focus on stenosis/calcification of the aortic valve and what medical interventions are currently used, how effective they are and how they could be improved through means of biomedical engineering.

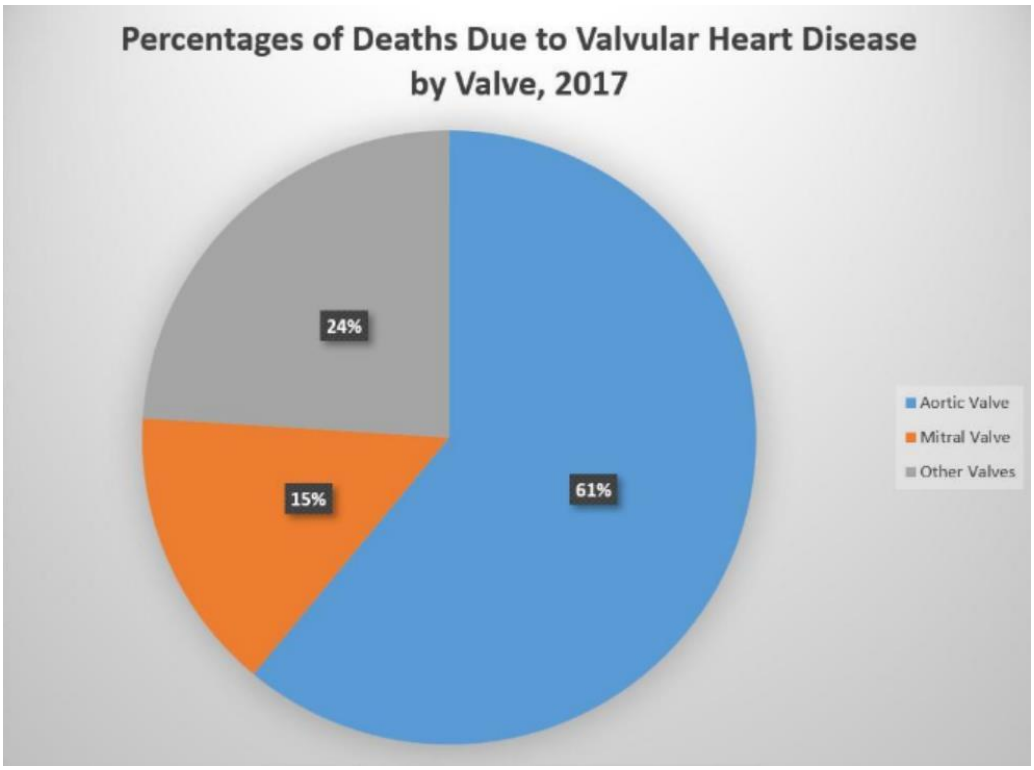

Figure 2. Percentage of deaths due to valvular disease, by valve, 2017. – data obtained from CDC, Atlanta, GA USA.[2]

Background of Aortic Stenosis

Calcification of a tri-leaflet is the most common cause of adult aortic stenosis, which is also considered to be a degenerative process that has many similarities to coronary artery disease; like lipid accumulation, inflammation, and calcification.[6] Calcification of a valve is a buildup of calcium on the leaflets that causes the valve to not function mechanically as it should, so in general this requires a mechanical solution like a valve replacement.

The typical patient symptoms related to aortic stenosis are angina (chest pains), dyspnea on exertion, syncope and potentially heart failure.[2] After the initial onset of these symptoms, the average survival of a patient is two to three years if not treated surgically.[6] However, for patients that are asymptomatic with even severe aortic stenosis have a much better expectation of outcomes.[6]

A primary diagnosis can be reached by performing a physical exam of the patient and observing a crescendo-decrescendo systolic murmur that can be heard at the base of the heart.[2] With this being an inaccurate and imprecise method, often a referral for a specialist will be placed.

Aortic valve stenosis is clinically diagnosed by an echocardiogram that is assesses the level of valve calcification, left ventricle, function and wall thickness.[3] An echocardiogram is performed by a technician in a doctor's office and is non-invasive; an instrument wand is moved across the chest and sometimes the ribs to capture images, measurements and videos of the heart while the patient is at rest laying on their back and occasionally their side. These images and videos are then analyzed by a cardiologist for diagnosis.

Symptomatic or severe aortic stenosis has a negative prognosis for quality of life and early intervention is strongly recommended for all patients; whether that is medical or surgical intervention.[3] If surgical intervention is not recommended based on risk vs. benefit of the procedure, it may be more appropriate to treat and mitigate the symptoms medicinally instead of surgically. However, medicinal treatments can only alleviate the symptoms and not the stenosis itself.[6]

Current Surgical Interventions for Treatment of Aortic Stenosis

For a patient diagnosed with aortic stenosis today a physician has two types of intervention that can be performed: TAVI, transcatheter aortic valve implantation, or SAVR, surgical aortic valve replacement. The success of either is heavily dependent on several factors relating to the patient's physical state and potential pre-existing conditions.

SAVR is the more invasive intervention, traditionally called "open-heart surgery", it tends to scare many patients. While TAVI only requires a small incision in the thigh to gain access to the femoral artery to travel to the heart. However, there are a few situations where SAVR would be the more appropriate method. For instance, a patient with difficult anatomy that would cause TAVI to introduce more risk than benefit, active or suspected endocarditis, thrombus in aorta or LV, or other valvular diseases in the neighboring valves.[3]

TAVI is generally the more favored intervention, being that it is less invasive and introduces less risk of infection and in general a shorter hospital stay. This method delivers the new valve through a catheter that is introduced in the femoral artery in the thigh. The incision is small and potential for adverse effects from surgery are minimal compared to that of a SAVR procedure. TAVI is also the optimal choice of intervention for those patients who are a high surgical risk, older in age, have had previous cardiac surgery, or situations where SAVR would not be possible.[3] See Table A1 for details about deciding factors for TAVI vs. SAVR presented in a 2021 guidelines publication from ESC, European Society of Cardiology. These guidelines are published and used by physicians world-wide to help determine which method of treatment may be the best course of action for a patient.

With TAVI being a relatively new strategy for the treatment of aortic stenosis, there was a need for additional studies and data to show its effectiveness and that it does not introduce

additional risk beyond what could be expected with the traditional route of SAVR. TAVI was first conceptualized in 1989, by Henning Rud Andersen, when he theorized that it would be possible to implant a heart valve percutaneously by catheter technique without surgery.[7]

Results of Current Medical Interventions

Between SAVR and TAVI there have been several studies to compare the short-term and long-term outcomes of the procedures. To be able to answer the question of whether or not TAVI is generally a better choice over the traditional standard of care SAVR procedure.

In the NOTION trial, published in 2021, an analysis was performed on the eight-year outcomes for patients with aortic valve stenosis that were at low surgical risk. The patients were randomized to either a SAVR or TAVI procedure. The findings were that there were no significant differences in the risk for all-cause mortality, stroke, or myocardial infarction.[8]

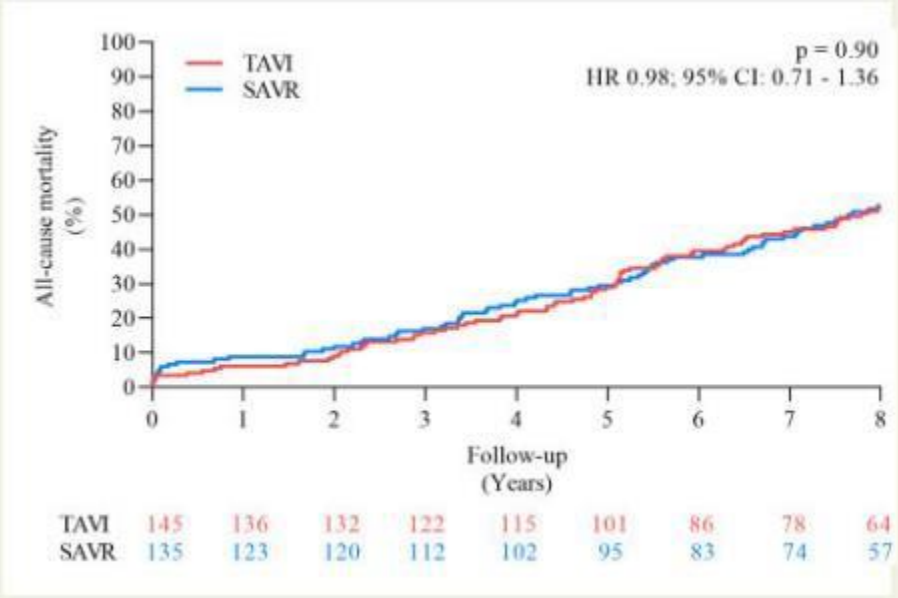

Figure 3. Estimated risk of all-cause mortality.[8]

In a meta-analysis performed and published in the ESC, several randomized clinical trials, RCTs, relating to SAVR versus TAVI for symptomatic severe aortic stenosis were reviewed. From this

meta-analysis they were able to conclude that TAVI is associated with a reduction in all-cause mortality and stroke up to 2 years irrespective of baseline surgical risk.[9]

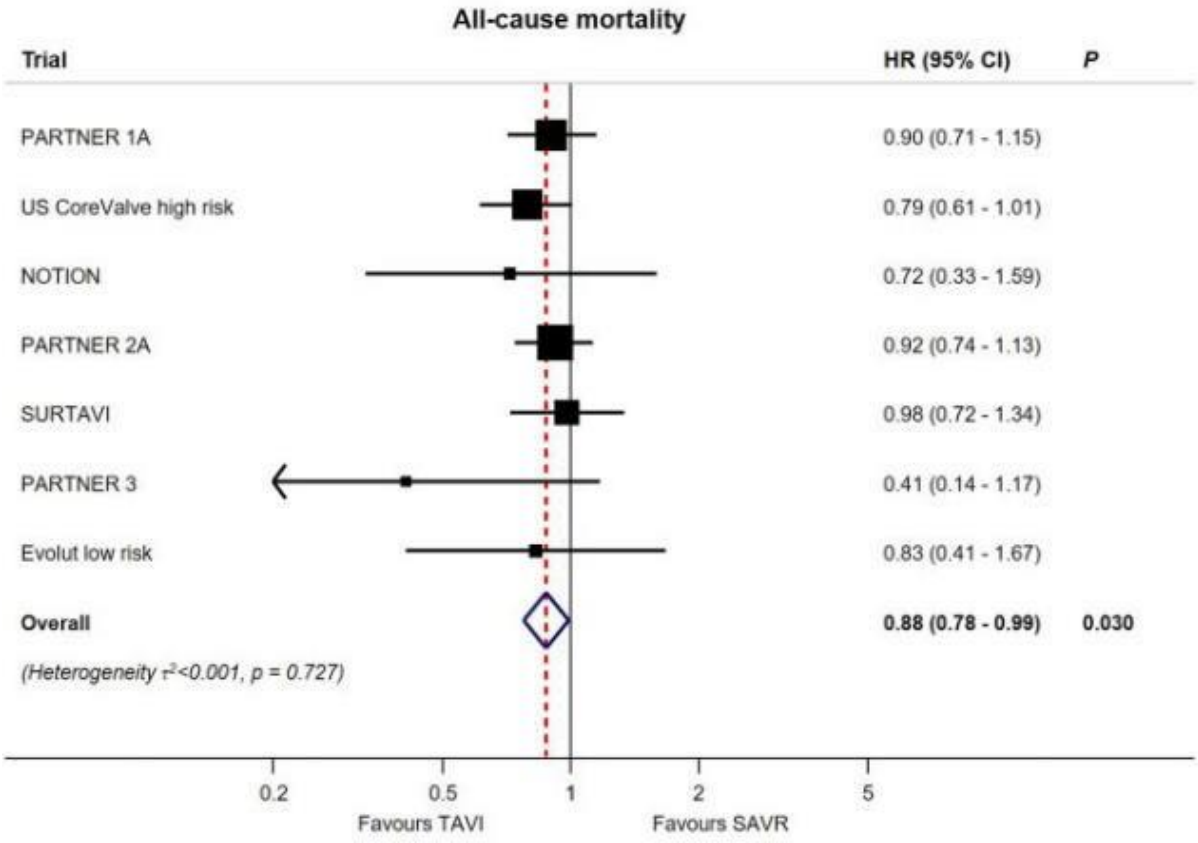

Figure 4. Meta-analysis for the primary outcome of all-cause mortality for the TAVR vs. SAVR replacement up to 2-year follow-up.[9]

The individual studies and meta-analysis are able to conclude that TAVI/TAVR does not introduce additional risks or harms to the patient and are able to conclude that this strategy actually lessens risk for all-cause mortality. For this reason, there has been great focus on developing medical devices specific to this surgical strategy. With this being a relatively new surgical route, there is tremendous room for medical device innovation to further the success of TAVI/TAVR procedures.

HEART VALVE MEDICAL DEVICES

The first-in-human feasibility study with a TAVR device was performed in 2002, by the start-up company PVT in collaboration with ARAN R&D.[4] As the TAVR valves moved from first-in-human studies to pursuing regulatory approval for use, it changed slightly in its indications for use over the first years of regulatory approval.

- 2011 – Indicated for use with inoperable patients with severe AS.[4]
- 2012 – Expanded to operable high-risk patients.[4]
- 2017 – Expanded for intermediate-risk patients.[4]

With new technology and devices being development, there is a constant need for regulation with patient safety being at the forefront of any innovation. For this reason, ISO developed a set of guidelines for the procedures related to heart valves implanted using the transcatheter technique: ISO 5840-3.[4]

Specifics on the Valve Medical Devices

For the treatment of aortic stenosis, AS, there are currently two general types of devices/materials cleared by the regulatory bodies for treatment. These are either biological tissues or mechanical components.[10] The use of biological valves started in the 1960's through SAVR procedures.[10] Because these tissue valves have been used since the 1960's, there has been a substantial amount of time for innovation and improvements to be made to the device design to improve patient outcomes.

The main benefit to using a biological tissue device compared to the mechanical device, is the patient will not have to be on continuous anticoagulation therapy.[10] Typical mechanical heart valves are made out of a carbon based material, which has shown to be susceptible to

thrombus and clotting on the device, which required physicians to also prescribe anticoagulation medications along with these valve treatments. Anticoagulation therapy is life-altering for most patients as it introduces a substantial bleeding risk to the patient. This is needed when using a mechanical valve because it is prone to calcification and build-up, which can greatly affect the opening and closing of the valve doors. One major set-back for the mechanical valve is the use of valve doors, because it is not possible to have leaflets with a solid material. Leaflets need to be able to move similar to how a windsock flaps in the wind.

Device Design Short-Comings

Even though TAVR is generally an improvement over SAVR, there have been some observations made relating to patient risks once TAVR became more widely used with younger and lower-risk patients. The most common complications relating the TAVR within this patient pool are: paravalvular leak, structural valve deterioration, SVD, permanent pacemaker implantation, valve thrombosis and strokes.[4]

In general, the biological valve design is favored over that of the mechanical counterpart, however this heavily depends on the patient's current condition as well as any pre-existing conditions that may or may not be related to the heart. See Table A2.

SVD is a permanent intrinsic change of the valves structure by means of calcification, pannus or leaflet failure.[4] With SVD being related to the device and patient age, there exists opportunity for device improvement to mitigate these risks and outcomes for the patient. The expansion of the patient pool to include younger patients, means the devices must also accommodate for a longer implantation lifetime than had historically been seen with the average patient being of highly advanced age.

There is a need for the valve device to be able to perform with a higher durability for a longer period of time and to also ideally be more resistant to calcification. These areas of improvement for the device would have an immense impact on patient outcome.

Challenges Specific to Biological Materials

There are several inherent challenges to the use of a biological material for this type of device. The tissue needs to be harvested reliability and with good reproducibility, however the rejection rate of material is approximately 98%.[4] Typically the material used is bovine pericardium, which is harvested from slaughterhouses. With this being a biological material, we are also limited on how much is available and the quality of what is available for use.

These device designs also require the tissue to be hand sewn onto the frame of the device. This introduces a high level of training needed for production as well as the human element to the reproducibility of the device. With each device needing a substantial amount of human interaction to be produced, it limits the manufacturing capability of how many devices can be completed in a timely manner compared to an automated production process.

While the devices that use tissue are generally preferred over the mechanical valves, there is still room for improvement of the material. Stepping away from a biologically derived material would open up a vast array of potential materials that could be designed to mitigate the durability and calcification issues observed with the tissue valves. There would also not be the limitation of the availability and expense of acquiring the base material similar to the challenges seen with biological acquisition.

If a polymer valve material were to be made in-house at a medical device company, there could potentially be substantial improvement made in the cost of the finished device. Depending on the cost to make the material as well as how much hands-on production would be needed.

Improvements Being Proposed and Studied

With a base valve material being made of polymers, it gives more freedom for the design and optimization of any potential limitations observed with the biological materials. From a paper published in 2018 however, it was stated that all attempts to date to develop a viable polymeric aortic valve have failed.[4] So far none have been successful enough in studies to gain CE Mark or FDA approval. Several companies are working on device designs and are seeing positive results thus far (2018): PolyNova x SIBS TAVR, Triskele urethane TAVR, and Endurance Valve HA-LLDPE.[4] See Figure A1 for current devices of varying designs and materials that have various regulatory approvals. Note that no polymer valves are currently approved for use in the United States, FDA approved, or Europe, CE Mark. Currently the only valves that are approved for use by either the FDA or CE Mark are made from bovine pericardium or porcine materials.

In 2018 the PolyNova group applied and received a NIH grant for their novel polymeric valve design research. This award was in the amount of $1,989,089 with a start date in 2020 and ending in July 2023. As of June 2022, the group released a publication on their progress so far. It was concluded that the durability of the leaflets reached 900 million cycles with no reduction in performance, with the FDA requirement of 200 million cycles for valve devices.[11] Their device design consists of a stent base material that is then covered with a “flexamer” material, avoiding the hand suturing of previous devices on the market.[11]

The PolyNova group has also been able to develop a method of injection molding the polymer over the base frame material. This eliminated a lot of human interaction in the process of attaching the material to the base frame and also potentially makes manufacturing of a valve substantially faster.

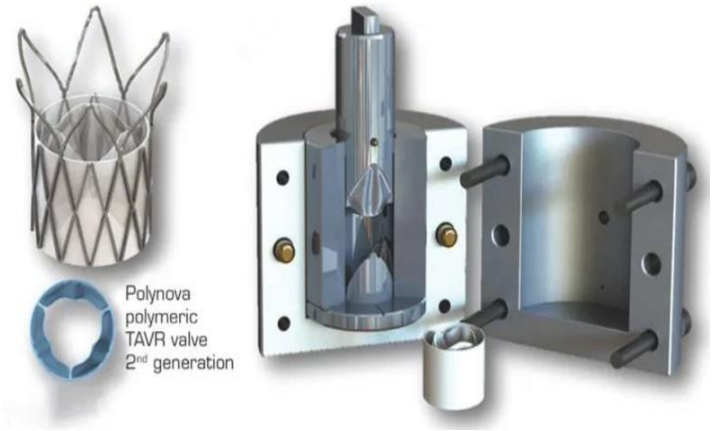

Figure 5. PolyNova valve design and injection molding manufacturing device. [12]

No updates regarding the Triskele urethane TAVR could be found beyond the initial publications from 2017.

No updates regarding the Endurance Valve HA-LLDPE from Ohio State University could be found beyond their initial publication in 2017.

Challenges for New Device Innovation

With many of the larger medical devices shifting from organic and in-house device development projects to acquiring small start-up businesses, the innovation of new devices is pushed to small start-up businesses and academic laboratories. With the limited number of companies and academic laboratories studying this specific device innovation, there is a large opportunity to break into the valve commercial space if a successful design were to be made.

Although the challenges for an innovation team would be the need to identify the right polymer that would fit all of the necessary criteria: biocompatible, durable at 200+ million cycles, resistant to calcification. Once the right polymer is identified, the team would then need to answer the question of whether or not the current frames of the device are appropriate as well as applications to the frame. Would it still need to be sutured on or could it be molded over the frame.

Figure 5 shows a series of valves currently being studied, both for SAVR and TAVR procedures. All of these valves are polymer based for the leaflet technology. Challenges specific to the TAVR valve compared to that of the SAVR valves, would be that the base frame needs to be able to compress and be placed inside of a delivery catheter. This is vitally important when considering polymer materials because the material will need to be able to e compressed and potentially folded over onto itself and be able to fully deploy and expand without sticking to itself.

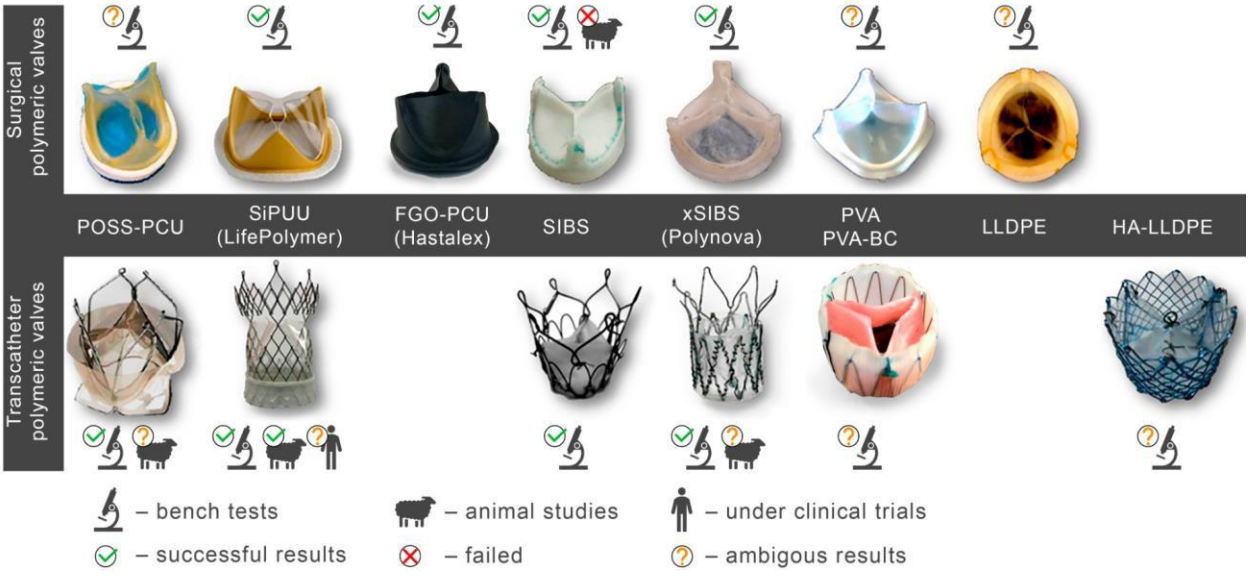

Figure 6. Series of valves currently being researched utilizing polymer technology for the leaflets.[13]

For a material to be a successful substitute for use from a biological tissue material, it needs to have several key attributes. The main attribute being that it has the ability to be stenosis/calcium resistant, to help prevent restenosis of the valve that would require additional medical intervention. The second most important attribute for a heart leaflet material would be tensile strength. The ideal state would be that the material performs similar or better than the normal heart tissue. Because tensile strength testing cannot be performed within a patient, it has been difficult to study this specific property. A research group was able to obtain these measurements by utilizing healthy human cadaver hearts. They were able to obtain data relating to the different tensile strength parameters.[14] It is important to note the differences seen between the pulmonary valve and the aortic valve, since this medical device has specific intentions for the aortic valve. Within figure 7, it can be observed that the porcine biological material performs below that of the normal human sample.

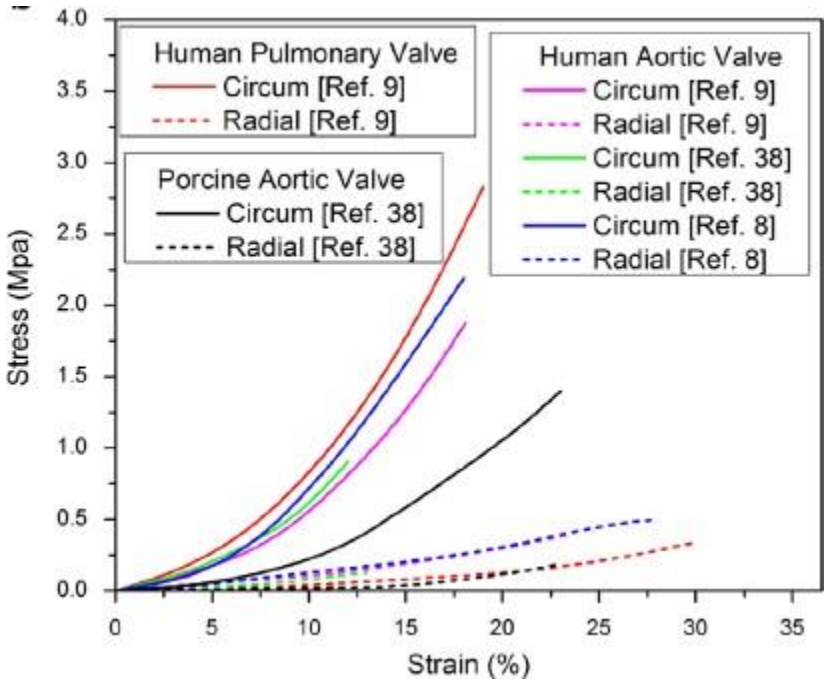

Figure 7. Uniaxial tensile stress–strain curves for human and animal models native aortic and pulmonary valves in circumferential and radial directions.[14]

Figure 8 shows the different phases of an aortic leaflet stress strain curve. This would be the ideal curve to match for a biomaterial, which would perform as well as a human heart and also outperform biological materials currently being used.

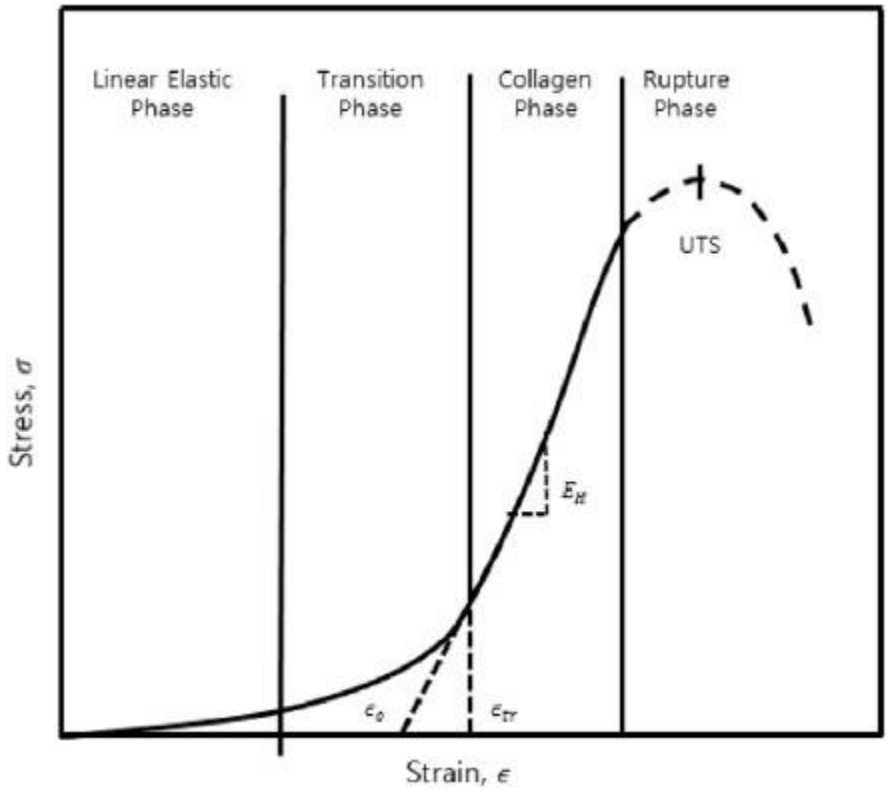

Figure 8. A typical uniaxial tensile stress–strain curve for soft biological tissues such as human aortic and pulmonary heart valve leaflets.[14]

While the FDA and other regulatory bodies do not have requirements for material performance, they do regulate the risk of intervention versus the benefit of intervention. As long as the benefit from the medical device and intervention are greater than if the condition remained untreated, the medical device is generally approved for use.

DISCUSSION

Proposed Valve Polymer Material

Besides the SIBS material currently being studied by the PolyNova group, one other polymer shows high promise for being a suitable substitute for biological tissue. The POSS-PU nanomaterial is a nanocage consisting of an inner organic framework of silicon and oxygen atoms and an outer shell of organic groups.[15] See figure 2A.

POSS itself is a bio-compatibilizer because of the Si-O bonds within its structure and when combined with hydrocarbons these materials are typically biocompatible because of the Si-O bond-induced chemical stability and surface property of being hydrophobic.[16]

While polyurethanes, PU, have been used in biomedical applications for a long time, their thrombus formation resistance is limited. Thrombus can potentially lead to strokes and blood flow restriction within the vasculature. Where POSS can help the PU material is in its ability to have variable surface tension, which has resulted in platelet and fibrin repulsion and has successfully increased thromboresistance of a biomaterial.[16] Thrombosis is the buildup of material, forming a clot, and calcification is when that buildup solidifies and hardens.

With the goal of a valve being resistant to calcification, it appears that the unique combination of POSS-PU would result in a calcification resistant material without requiring additional materials or coatings.

POSS-PU can be synthesized from methylene diphenyl diisocyante, trans-cyclohexanechloroydrinisobutyl POSS, and poly(carbonateurea) glycon, with a mixture of 40:1 (by wt.) ethylenediamine: diethylamine as a chain extender, see figure 7 below.[16]

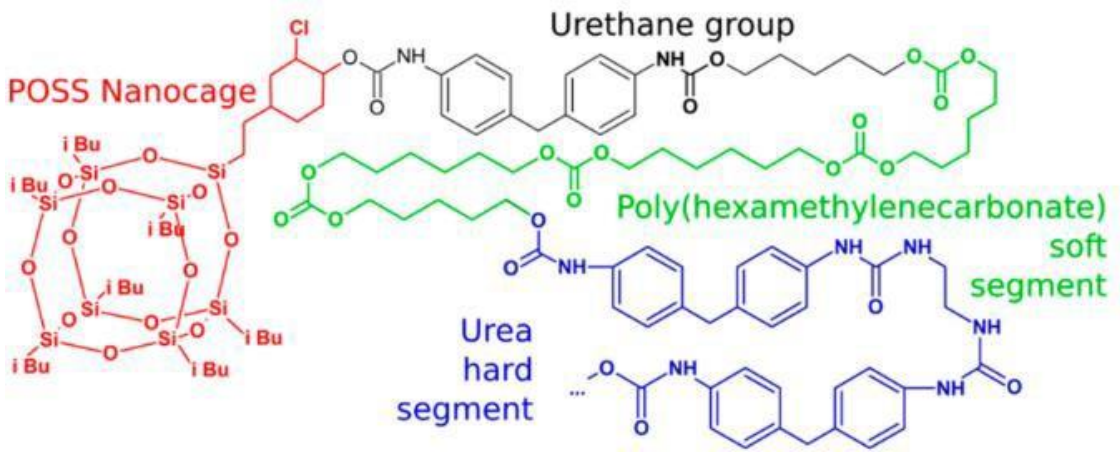

Figure 9. Structure of original PCU-POSS.[16]

From a publication in 2011, it was observed that with slight manipulation of the base POSS material there is incredible properties that make it a true game changer for biomedical applications such as hemocompatibility, antithrombogenicity, enhanced mechanical and surface properties, calcification resistance and reduced inflammatory response.[15]

Several studies have been performed specific to a POSS base material being used in biomedical applications where it showed a high potential for being successful; drug delivery, dental composites, biosensors and tissue engineering.[15] Because of the framework of this material and mainly consisting of Si-O and Si-C, it behaves similarly to a silicone material. Which has been used frequently in medical devices since the 1960's.

To meet the needs of a cardiovascular application, this research group developed a nanocomposite by introducing POSS moieties into poly(carbonate-urea)urethane; POSS-PU as a pendant chain.[15] From this study the group was able conclude that the new nanocomposite material has promising results for its cytocompatibility, antithrombogenicity and biostability.

Short 31-day studies were performed to access the nanocomposities resistance to calcification. From these studies they were able to conclude that the POSS-PU material was

more resistant to calcification than biological tissue as well as polyurethane alone.[15] Performing substantially better than the traditional biological tissue.

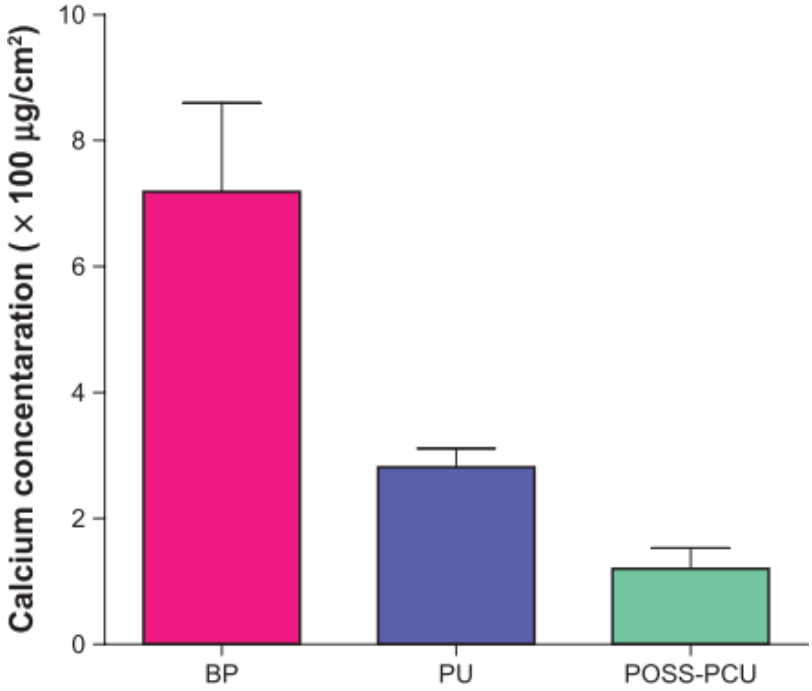

Figure 10. Chemical analysis of calcium deposition. BP, bovine pericardium; PU, polyurethane; POSS-PU, polyhedral oligomeric silsesquioxane-poly(carbonate-urea)urethane.[15]

This research group had developed a heart valve prototype using the POSS-PU material with a similar design to that of a tissue valve; suturing the material onto a frame. Although this design is not specific to a TAVI type of procedure, it still showed promising results for being a successful alternative to a tissue material.

Potential Research Setbacks

With the previously discussed POSS-PU material and specific group studies being performed on the material being published in 2011, a search of more current publications made relating to POSS, POSS-PU and this specific research group was made. However, no new or

additional studies relating to this material or this research group and their POSS work was found. A search utilizing PubMed was performed relating to the POSS-PU material; PubMed is typically where medical device industry posts device related publications. Only one article returns from the search, with it being a general article about POSS-PU material varieties. Nothing specific to the materials applications or testing related to medical applications.

It seems as though the only group making wide strides in the polymer valve space is the PolyNova group from the University of London. It is possible that medical device companies could be working on this internally and not publishing, keeping the intellectual property as insider knowledge for the moment.

CONCLUSION

It comes off odd that there were studies published showing so much promise for a polymer-based material for valve leaflets, for them to almost completely stop their progress. Without seeing studies or discussions stating their were issues or concerns about the material, it can be theorized that the issue could have been with research resources and what external factors could have contributed to the pause in innovation.

The studies were published around 2017-2018. A big factor that had global impact was the emergence of COVID-19 starting globally in 2019 and nationally in the United States in 2020. This would have had dramatic impact on in lab experiments with being on-site, sourcing chemicals and travel of people. I believe that the sourcing of chemicals could have been the most dramatic impact on research of this type. Both the impact of international/national shipping and the cost of chemicals and supplies in general.

Another COVID-19 factor to consider, many research laboratories changed their strategy to focus on devices and solutions relating to COVID-19 treatments and hospital needs such as ventilators and PPE supplies.

With no device being available on the market nor moving towards clinical studies, there is still room for innovation and device advancement for a research group. Even if PolyNova shows great success with their bench studies, the success of their device will be determined by clinical studies.

In the theoretical situation of unlimited funding, unlimited time and resources. I would pursue a POSS-PU material and explore if it could be injection molded over a TAVR/TAVI delivery frame. The POSS-PU material showed great promise in performing similar to tissue with the added potential to also be drug delivering. Current tissue valves do not have the ability

to deliver drugs to the site, adding this to a device can help reduce potential adverse outcomes for the patient.

If this material is able to be injection molded over a frame, the manufacturing process is exponentially simplified from having a person hand suture tissue to the frame. This also reduces valve to valve variability with a machine building the valves instead of a human touch.

I believe there is a large hole in the structural heart valve industry that could have a substantial impact on patient care and quality of life outcome.

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APPENDIX

Figure A1. Selected TAVR valves based on varying design approaches, both commercially-available and under-investigation devices. [12]

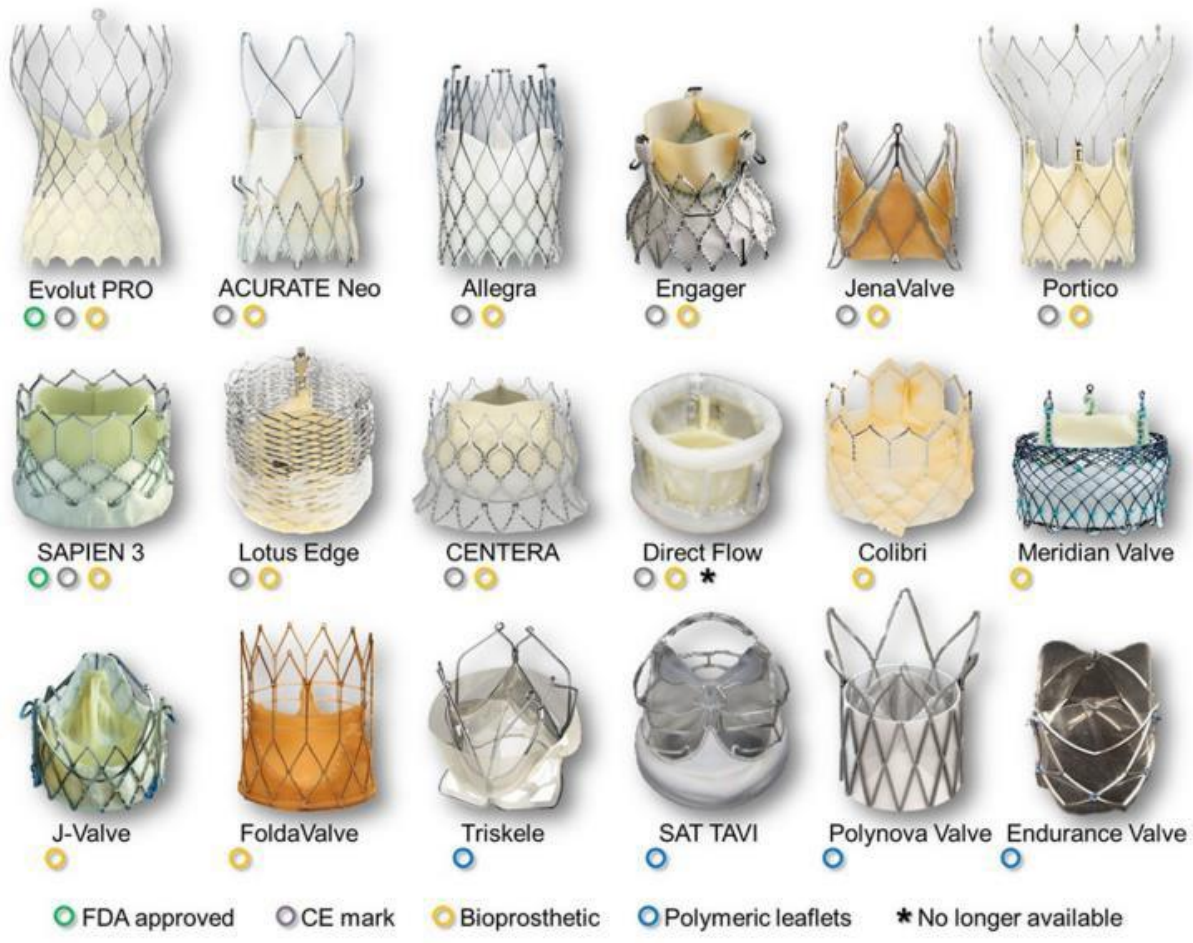

Figure 2A. Different structures of silsesquioxanes: Ladder (A), partial cage (B), cage (C)[16]

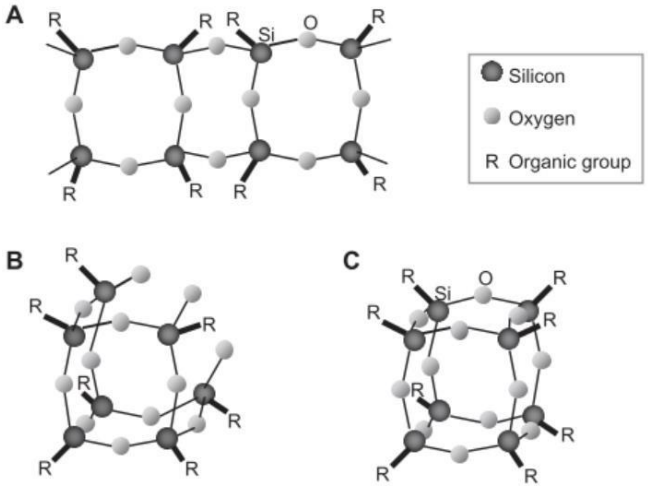

Figure A3. Clinical, anatomical, and procedural factors that influence the choice of treatment modality for an individual patient. As presented in a 2021 Guidelines for the management of valvular heart disease from the ESC.[3]

	Favours TAVI	Favours SAVR
Clinical characteristics		
Lower surgical risk	–	+
Higher surgical risk	+	–
Younger age[a]	–	+
Older age[a]	+	–
Previous cardiac surgery (particularly intact coronary artery bypass grafts at risk of injury during repeat sternotomy)	+	–
Severe frailty[b]	+	–
Active or suspected endocarditis	–	+
Anatomical and procedural factors		
TAVI feasible via transfemoral approach	+	–
Transfemoral access challenging or impossible and SAVR feasible	–	+
Transfemoral access challenging or impossible and SAVR inadvisable	+[c]	–
Sequelae of chest radiation	+	–
Porcelain aorta	+	–
High likelihood of severe patient–prosthesis mismatch (AVA <0.65 cm^2/m^2 BSA)	+	–
Severe chest deformation or scoliosis	+	–
Aortic annular dimensions unsuitable for available TAVI devices	–	+
Bicuspid aortic valve	–	+
Valve morphology unfavourable for TAVI (e.g. high risk of coronary obstruction due to low coronary ostia or heavy leaflet/LVOT calcification)	–	+
Thrombus in aorta or LV	–	+
Concomitant cardiac conditions requiring intervention		
Significant multi-vessel CAD requiring surgical revascularization[d]	–	+
Severe primary mitral valve disease	–	+
Severe tricuspid valve disease	–	+
Significant dilatation/aneurysm of the aortic root and/or ascending aorta	–	+
Septal hypertrophy requiring myectomy	–	+

Figure A4: Factors that contribute to favoring a specific type of prosthesis in patient's stenosis of the aortic (+) or that militate against using a particular type of prosthesis (-).[3]

Factor	Mechanical prosthesis	Biological prosthesis		
		Conventional	"Rapid deployment"	Transcatheter (TAVI)
Age <60 years	+	–	–	–
Age 60–65 years	No unequivocal treatment recommendation currently			
Age 65–75 years	–	+	+	–
Age >75 years	–	+	+	+
STS score >4%	–	–	+	+
Life expectancy <10 years	–	+	+	+
Already requires anticoagulation*[1]	+	–*[1]	–*[1]	–*[1]
On hemodialysis	–	+	+	+
Endocarditis	+	+	–	–
Contraindication for phenprocoumon*[2]	–	+	+	+
Bicuspid aortic valve	+	+	+*[3]	–*[4]
Porcelain aorta	–	–	–	+
Patient has had previous bypass surgery; at risk of bypass injury from reoperation	–	(+)	–	+

In some clinical scenarios (for example, anticoagulation for atrial fibrillation) it may make sense in spite of existing anticoagulation to implant a biological prosthesis.
For example, limited compliance, women wishing to become pregnant, high risk of hemorrhage, etc.; *[3] Classification according to Sievers: 1 & 2; *[4] Classification according to Sievers: possibly 1;
TS, Society of Thoracic Surgeons; TAVI, „transcatheter aortic valve implantation"