Ethical considerations relating to different types of heart valve prosthetics

Abstract

With the increasing global population and average lifespan more people suffer from age associated diseases such as cardiovascular disease. In some cases the disease can be treated with novel medical devices such as pacemakers but for others transplantation remains the only viable option. This is often the case for patients with heart valve failure. However, there is a worldwide organ shortage for transplantation. This has led to the development of different types of heart valve prosthetics. Mechanical heart valves are durable but increase the risk of thromboembolism, resulting in patients needing to take lifelong anticoagulant therapy which has severe side effects. Patients with bioprosthetic heart valve prosthetics do not need to take anticoagulant therapy but risk repeated open-heart surgery because bioprosthetic heart valves are less durable. Tissue-engineered heart valves are newest to the market but have not yet reached their full potential and are therefore not yet frequently used. The development of these different types of heart valves has led to multiple different ethical discussions. Here, we will discuss which types of heart valves have given rise to which ethical considerations and whether these discussions have ceased or remain applicable with the development of new types of heart valve prosthetics. In particular we will try to gauge whether past and current ethical discussions regarding heart valve prosthetics will be applicable to the future regenerative tissue-engineered heart valves which are not yet commercially available.

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Laymen summary

The average lifetime of people has increased significantly over the past decades. This has caused age related diseases to increase as well. A frequent age related ailment is heart valve failure. The heart contains four pairs of heart valves, which ensure that blood will flow in the right direction. Failure of one of these valves can lead to complications such as heart rhythm abnormalities, blood clot formation or a stroke. To prevent this, a failing heart valve needs to be replaced. Because there are not enough heart valves available for transplantation, heart valve prosthetics have been designed. The earliest heart valve prosthetics were made out of metal and are referred to as mechanical heart valves. These types of heart valves are still in use because their durability makes them the most suitable for younger patients. Elderly usually receive heart valve prosthetics from pigs or cows, bioprosthetic heart valves, because bioprosthetics have less side effects than mechanical prosthetics. Currently heart valves are being developed in the lab using scaffolds and human tissue to create a more optimal prosthetic: the tissue-engineered prosthetic. These different types of heart valves have led to different ethical questions and debates. For example, is it ethical to use animal organs to benefit a human? In this report an overview of the different ethical debates, surrounding the different types of heart valve prosthetics, found in published academic literature is given. Also the relevance of the debates is considered in the light of the other types of prosthetics, (i.e. are the same ethical debates relevant for different types of heart valve prosthetics) and the current time spirit (i.e. are older ethical debates still relevant?).

Introduction

There is a worldwide organ shortage for transplantation. Waiting lists keep growing and it is estimated that the demand for organ transplantation will increase with 15% each year[1,2]. There are a plethora of causes leading to the need of organ transplantation, one of which is cardiovascular disease. This overarching term includes heart failure, arrhythmia and complications with the heart valves. In some cases the disease can be treated with novel medical devices such as pacemakers but for others transplantation remains the only viable option.

This is often the case for patients with heart valve failure. The aortic and pulmonic valve separate the ventricles from the arteries, which they are named after, this prevents blood from flowing into the body when the atria contract to fill the ventricles with blood (figure 1). The tricuspid and mitral valve separate the ventricles from the atria to prevent blood from flowing back into the atria when the ventricles contract and pump blood into the body (figure 1). The valve can fail by not opening properly, stenosis, which leads to the heart needing to work harder to pump around enough blood[3]. It is also possible that the valve does not close properly, regurgitation, which leads to blood leaking backwards[3]. Both forms of failure can be congenital or caused by cardiovascular disease.

A replacement of the valve is usually the only treatment option, due to donor shortage different types of prosthetics have been developed over the years. In 1957 the first mechanical heart valve prosthetics was marketed: the Starr-Edwards Ball-valve[4] (see Fioretta et al.[5] for in-depth review about different types of heart valves). A plus of the mechanical heart valve is that you do not need a donor. However, the risk of

thromboembolism increases significantly which means that patients with a mechanical valve prosthesis need to take lifelong anticoagulation therapy which has severe side-effects such as bleeding. Over the years a multitude of mechanical heart valves has been developed (e.g. tilting-disc and bileaflet design) with better flow dynamics and lower failure rates, although the risk of thromboembolism remains. Nowadays it is estimated that 55% of the heart valve transplants are mechanical, with the remaining 45% being bioprosthetic transplants[6]. In 1965 the first porcine heart valves were transplanted to humans[7,8]. Recipients of bioprosthetic valves do not need to take anticoagulation therapy but the valves tend to have a shorter lifespan than mechanical valves. Other bioprosthetic heart valves include transplants from oneself (autograft) or a donor (homograft). These transplants are less common because of the donor shortage and the need to replace the heart valve which has been used as an autograft. Thus bioprosthetic heart valves usually refer to porcine valves, although valves have also been made out of bovine pericardium or veins.

Currently, tissue engineered heart valves are being developed for clinical application. These valves consist of polymers that were designed to combine the immunocompatibility seen with mechanical valves and the physiological shape of bioprosthetic valves[9,5]. Types of polymeric valves have been on the market since the 2000's but its full potential has not yet been reached[5]. The aim of tissue engineered valves is that they can repair, remodel and regenerate when transplanted so that patients no longer need anticoagulation therapy or repeated open-heart surgery[5].

With the increasing global population and average lifespan more people suffer from age associated diseases such as cardiovascular disease. In 2020 182.000 patients received a type of heart valve transplant in the United States, this number is expected to surpass 240.000 in the next five years[10]. Besides, cardiac surgery is not widely available in developing countries, indicating that the actual number of required valve transplants is greater[11]. Since there is a donor shortage and both mechanical and bioprosthetic valves have significant downsides there is still a need to develop improved valve prosthetics. At present there is also no suitable treatment option for children and young adults, because mechanical valves are too big and bioprosthetic valves need to be replaced frequently.

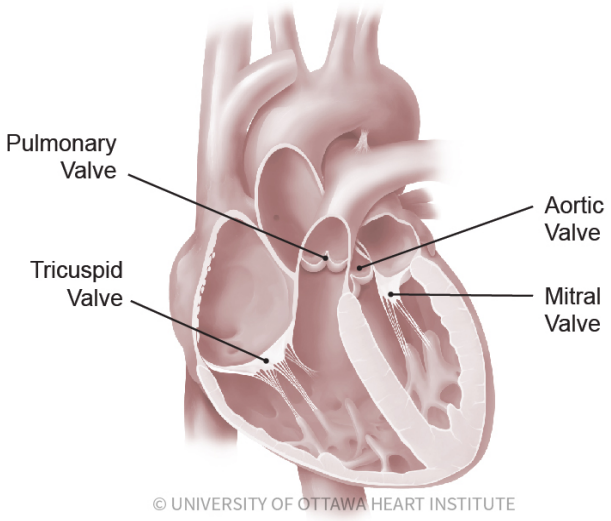

Figure 1. Intersection of the human heart. The human heart contains four different heart valves, two that separate the atria from the ventricles (tricuspid and mitral valve) and two

that separate the ventricles from the veins (pulmonary and aortic valve). Source: University of Ottawa heart institute www.ottawaheart.ca.

Both the development of valves and changing societal perspective lead to different ethical discussions. Are patients properly informed about the possible side-effects of their treatment? When is a new medical device safe enough to market? Is it ethical to farm pigs and cows for their organs? These and more questions arose during the history of valve development and are expected to emerge with future progress. Perhaps other discussions have ceased due to the same scientific progress. Here we aim to give an overview of the different ethical discussions that have emerged and disappeared with the development of different types of heart valve prosthetics and if these discussions are applicable to tissue-engineered heart valves. Academic literature was consulted to identify past and present ethical discussions[1*]. Both the existence and lack of discussions relating to the different types of heart valves were taken into consideration. First ethical discussions about mechanical valves will be specified, followed by the deliberation whether these discussions are still relevant for bioprosthetic and tissue engineered heart valves. This will be repeated for bioprosthetic heart valves. Finally, we will focus more in depth on the relevance of the identified discussions regarding tissue engineered heart valves, since these valves are not yet commercially available and new ethical discussions will likely arise in the near future. We find widely differing discussions that remain mostly unresolved, though required improvements are suggested.

[1*] The literature search was conducted in Google Scholar using several search terms. The search term always included valve*, a term to filter on ethical debates: (ethic* OR moral* OR bioethic* OR social* OR societal*), and a term to filter for a specific heart valve type: (mechanical OR metal OR prosthetic) or (bioprosthetic OR pig OR porcine). Sometimes extra search terms were added (e.g. ‘human rights’, ‘heart’). Example of a complete search term: valve* AND (ethic* OR moral* OR bioethic* OR social* OR societal*) AND (mechanical OR metal OR prosthetic).

Mechanical heart valve

Mechanical heart valves were the first commercially available heart valves to replace failing human valves[5]. With time newer types with improved shape and physiological properties have been marketed. The biggest concern of mechanical heart valves is that patients need to take lifelong anticoagulant therapy to reduce the increased risk of thromboembolism. Anticoagulant therapy has severe side effects which complicate the patient's life. Nonetheless, mechanical heart valves are still in use[6]. Why mechanical heart valves are sometimes chosen over bioprosthetic heart valves will be discussed in the section Availability. First we will focus on two past cases of ethical misinformation regarding mechanical heart valves and their applicability to newer types of heart valves.

Patient knowledge and misinformation: Warfarin

Warfarin is a type of anticoagulant therapy for patients with mechanical heart valves. Warfarin is a complex therapy to manage because it can have serious side effects, most importantly: bleeding. This can be minor, for example prolonged bleeding from a cut or nosebleed, or more serious such as bleeding from the gums when brushing your teeth or between menstrual periods. Even more serious are the rare cases of internal bleeding. Besides the increased risk of bleeding, warfarin also poses a complex therapy because it has a narrow therapeutic window. This means that warfarin has a small range of being effective without having toxic side effects. Patients are therefore subjected to regular blood tests and the exact dose is patient specific. Lastly, patients need to regularly take vitamin K because warfarin is a vitamin K antagonist. All in all the response to warfarin differs greatly between patients and successful treatment depends on the patient's knowledge[12]. Worryingly, multiple studies have shown that a majority of the patients have insufficient knowledge about their anticoagulation therapy after discharge. Especially older patients, patients with a lower family income, unemployed patients and patients with a lower education level have less therapy knowledge[13]. The same study shows that patients are in need of an education program that builds on the information provided by the hospital, such as a community counselor or an education program for discharged patients[13].

The lack of warfarin knowledge among patients has been studied and described in multiple different countries and among patients with varying socioeconomic statuses[13–15]. Noteworthy is that none of these papers discuss the ethical implications of the lacking knowledge of patients undergoing life changing treatment. Among patients receiving cardiovascular implantable electronic devices (CIEDs) a lack of education about life after the procedure is also observed. Here, we will discuss some of the ideas of nurses who try to explain why patients receive too little information to compare this with the warfarin situation.

In an interview study with fourteen nurses about CIEDs, all agreed that the informed consent process was too focused on the procedures whilst instructions on living with the device were lacking[16]. Patients with CIEDs risk infection of the device and receiving inappropriate shocks from the device. The nurses explain that these types of implantation specific complications were only superficially described to the patients before undergoing the procedure. Secondly, the interviewed nurses describe a doctor-patient dynamic in which the patients trust the doctor and do not question their doctor's recommendation. According to the nurses, doctors almost always recommend the implant, sometimes even with a fear inducing method: if you

do not get the implant you will die! Doctors also seem to feel a certain responsibility to make the patient feel at ease, thereby downplaying possible side effects. The nurses say that many patients feel like they do not have a choice whether to continue with the procedure, it is a must. Once patients have received their CIED they are confronted with the accompanying risks. Besides the doctor-patient relationship, family also plays an important role. Especially for older patients, family members can put pressure on patients to accept an implant, maybe without considering the life of the patient itself after transplantation. One nurse gives an example of a patient for whom the side effects of an implant were not clear and who was inclined to receive an implant because his son and doctor agreed it was best. When the patient received two shocks after the procedure, he wanted the implant to be turned off. This raises the idea that if the patient had been better informed he would have made a different decision.

If we compare these observations with the warfarin situation described before we see that there is a similar lack of patient education regarding life after the procedure. Of course life after the procedure differs substantially for CIED patients and heart valve transplant patients. However, both are expected to alter their lifestyle choices (e.g. less excitement for patients with a heart implant and a vitamin K rich diet for patients taking warfarin). It seems unlikely that warfarin misinformation is due to a lack of information sources before treatment as suggested by the nurses as cause for lacking CIED information. As discussed, patients that have received warfarin information in the form of a leaflet, video or counselling session have no better warfarin knowledge than patients who did not[13]. Thus this information about life after the procedure does not inform all patients equally. There seems to be a need for a different form of education (e.g. tailored counseling) or more guidance after the procedure. We lack data to properly assess if the other reasons suggested by the nurses are causing the lack of knowledge, but since they are general (trust in doctors, familiar influence) it seems probable that they apply to some degree.

All in all we observe that even with available education it is possible that patients are not able to make a considered decision. It could be argued that patients are responsible for their level of understanding and choose not to make an informed decision. But we are now aware of this lack of knowledge, especially among patients with lower incomes and lower general education[13], which implies that the available education is not sufficient for all patients. Thus by measuring the patient's knowledge levels we create the obligation to improve education on warfarin. Besides, we value that patients can give informed consent and are able to make autonomous decisions[17,18]. Even when patients are vulnerable and suffer from a life threatening disease the consequences and risks accompanying a possible therapy should be made clear and not be sugar coated. To achieve this there needs to be a focus on creating a neutral environment where patients can ask questions and will be presented with treatment risks and side effects. In this environment we need to pay attention to the patient's understanding of the accompanying consequences to ensure that he can make the best decision for himself. The nurses observed that patients receiving the same procedure can have varying interpretations[16]. Some recognize the implant as their guardian angel that saved them from death whilst others regard it as a ticking time bomb waiting to shock them[16]. This highlights the different interpretations of patients when presented with the same risks. We must not forget that the patients differ from each other and might be in need of different educational methods.

Patient knowledge and misinformation: Bjork Shiley

The need for anticoagulant therapies such as warfarin was reduced with the development of new mechanical heart valves by Bjork and Shiley in 1979. Due to the valve's innovative convexo/concave shape, the risk of blood clotting was significantly lower compared to other mechanical valves[3,19]. However, there is a controversy related to the Bjork Shiley valve which has to do with misinformation and lack of patient knowledge that we will discuss here. Bjork Shiley valves were being transplanted without thorough clinical testing, a process referred to as earning whilst learning[20,21]. When more Bjork Shiley valves were being transplanted also more cases of its failure were reported. Even though the total number of failures remained relatively low (below 1%[21]), all valve failures seemed to be caused by a similar fracture, indicating a design or manufacturing error[20]. In response to these valve failures the manufacturer, Shiley Inc., decided to retract valves that were not yet implanted and to send surgeons a letter informing them about the chances of valve failure. Patients were not contacted directly, it was up to the surgeon to decide whether to inform patients or not. According to Shiley Inc. the risk of explantation was bigger than valve failure and therefore informing patients would only lead to unnecessary and harmful anxiety.

Fielder explains that this reasoning is invalid and unethical[20]. Firstly, the deaths due to valve failure were underreported by including only known deaths. Both valve and heart failure have similar symptoms, an autopsy is required to assess the cause of death. It is estimated that the number of deaths caused by valve failures is 50% higher than reported[22]. Shiley Inc. also overstated the risk of explantation by combining the mortality rates of elective and emergency surgery, whilst the risk of elective surgery is significantly lower. Even if explantation poses more risk than valve failure, it is still the patient's right to decide whether or not to take the greater risk. A number of patients have chosen to explant their heart valve once they were informed of both risks[23]. Apart from medical decisions, knowing that your heart valve is subject to failure has important implications for your personal life and choices. Patients for example chose to reside near hospitals capable of open heart surgery and evade air travel and remote areas. Lastly, Fielder argues that the generally accepted idea about informed consent is that patients should be enabled to make the best informed choice and that the role of the healthcare professionals is to make sure that patients can make this informed choice.

Fielder also shows that the undertaken steps by Shiley Inc. to inform the medical community were lacking[20]. The letter addressed to the surgeons contained promotional statements to sugarcoat the valve’s failures, and failure rates were noted as decimals (0,00021 failures per year) which are more difficult to interpret than incidences (2.1 failures per 10.000 transplants per year) and percentages (0.021% failures per year). Also, surgeons rarely see their patients after surgery which minimizes the likelihood of the doctor informing their patients even further. With this emphasis on letting doctors decide about providing information about valve failure, many patients learned about their heart valve risk via TV shows and/or newspapers discussing the Bjork Shiley allegations. It is improbable that this is a better way of informing a patient than via the manufacturer or their personal doctor. As a direct result of the Bjork Shiley lawsuits a new legislation was passed to make sure that both patients and doctors are notified by the FDA, the Food and Drug Administration, in case of a newly discovered risk or malfunction of a critical device such as a heart valve. Fielder notes that

this is already a major improvement, but proper information supply still depends on the willingness of the ones who can act upon it, in this case the FDA.

Thus Shiley Inc. misinformed the medical community about the heart valve's risks of failure and chose to withhold this information all together from their patients. Both in the warfarin case and the Bjork Shiley case there are patients that choose the greater risk when confronted with the side-effects: turning off their device or explanting their heart valves. These patients would probably have made different decisions if they were presented with all pro's and con's regarding their treatment beforehand. The risks of the Bjork Shiley valve only became apparent when the valve was already on the market which indicates that more clinical testing beforehand is desirable (also see section Bioprosthetic valves, clinical trials). Owing to this incident the FDA is now responsible for informing patients and the medical community of newly discovered defects of a device and thorough clinical testing is now the norm. Both measurements help prevent the same scenario from repeating itself with bioprosthetic and tissue engineered heart valves. Indeed, we see little to no discussion regarding misinformation and lack of patient education regarding these newer types of non-mechanical heart valves.

Availability

Due to the controversy surrounding the Bjork Shiley heart valve, Shiley Inc. withdrew the valves from the market even though an improvement of the welding technique resulted in no further fractures of the valves[21]. Before the welding change the failure rate of the Bjork Shiley valves had been estimated around 0.5%[21]. There is no specific threshold for medical devices to be withdrawn from the market, just like there is no specific type of defect or scale of how serious the defect needs to be to be withdrawn from the market. For example, in a survey half of the participants noted that they were disturbed by the sound of the implanted Bjork Shiley valve[24]. Is this a serious enough defect to withdraw the valves from the market? According to Fielder the withdrawal of the Bjork Shiley valve is justified because of their unethical way of informing the medical community and patients[21]. He argues that the device was not defective due to its failure rate or disturbing sound but due to the unethical practices that surrounded the marketing and development of the device. Fielder believes that if Shiley Inc. would have temporarily removed the valve from the market to correct the structure subject to fracture that the Bjork Shiley valve would still be available today.

With the development of bioprosthetic and tissue-engineered heart valves the need for mechanical heart valves has decreased but they are still favoured for younger patients. Mechanical heart valves are more durable than bioprosthetic heart valves, which tend to calcify and then be rejected from the body[25]. In a recent case report it was shown that a patient still had a working Bjork Shiley valve 40 years after transplantation[26]. For younger patients it can be safer taking lifelong anticoagulant therapy than repetitive open heart surgery to replace calcified heart valves. With Bjork Shiley valves already having a low failure rate, likely an even lower rate after adjusting the welding technique, it could well be that the Bjork Shiley valve would have been the most successful mechanical heart valve on the market today.

Most literature that discuss the availability of medical devices do not focus on heart valves specifically but consider the marketability of medical devices (when is good good enough),

the cost of medical devices (allocation of healthcare funds and patients with lower socio-economic status) and finally the conflicts of interest (commercial interest of the device developer and/or health professional) in a more general manner. Here we will briefly address the applicability of these discussions to heart valves.

When a medical device is being developed the decision needs to be made to either start using the medical device in practice or to invest more in testing and development. Citron argues that early application of the pacemaker has resulted in a current standard treatment option for patients with bradycardia[27]. He also acknowledges that there were limitations and complications which should have kept the pacemaker off the market until the device was perfected. Similar arguments relating to the Bjork Shiley heart valves have been discussed. As Fielder also mentioned, there is no clear boundary when a device is good enough[21]. The problem does not only apply to new medical devices coming onto the market but also applies to improvements of already available medical devices. To reduce the risk of bacterial infection of the heart's inner lining, the endocardium, it was tried to add a thin silver lining to the heart valve. Silver is known to have antibacterial properties. Therefore it was thought that it would prevent infection of the endocardium. However, the leak incidence around the transplanted valve increased significantly resulting in patients needing open heart surgery to replace their silver heart valve[28]. Perhaps more clinical trials would have revealed this complication and prevented wide application of the silver heart valves. As Citron puts it, there is a dilemma of how high the bar for safety and effectiveness must be set for both new medical devices and product improvements[27]. If the bar is set too low we risk complications as seen with the silver heart valve. If the bar is set too high patients might miss out on innovative medical devices which might aid them significantly. It remains an ongoing discussion when medical devices are ready for the market. For mechanical and bioprosthetic heart valves there are versions on the market already, which set the bar: newer models need to improve either their effectiveness or safety (or both) to be able to replace the current models. Some tissue-engineered heart valves are commercially available but the expected tissue-engineered valves that are able to repair, remodel and regenerate are not. The novel nature of these regenerative valves demands a new, different way of testing and they are subjected to the ongoing discussion of when good is good enough.

Hutchison and Sparrow also discuss ethical concerns of ongoing development of medical devices, specifically pacemakers[29]. They argue that with newer models of medical devices the knowledge and education of health professionals needs to keep expanding which increases costs. It also affects the ability of hospitals to help patients in emergencies because they need to possess the knowledge of their specific device. This increasing complexity of ongoing development affects both the availability of medical devices and proper patient care. Besides, manufacturers have commercial interests which will not always align with patients' needs, thereby increasing costs for the patient and/or their healthcare provider. This conflict of interest can also arise when a surgeon or patient becomes brand loyal[29,30]. When a surgeon’s training and education is financed by a manufacturer the surgeon will presumably use their medical device more often than a competitor's device. This can lead to continuous pursuit of innovation without properly taking the patient’s risks and costs into account. Likewise, patient’s can become brand loyal because they form a relationship with technicians employed by the manufacturer who look after their device, thus blurring the line between personal interest and sales[29]. Hutchison and Sparrow stress that we need to discuss these types of ethical concerns, preferably before new ones arise,

because complexity will only increase with the development of more medical devices[29]. Their concerns can be applied to heart valves, since the amount of types do increase and conflicts of interest do occur (e.g. Bjork Shiley valves). However, heart valves themselves are not complex medical devices like pacemakers or complete organ substitutes. Thus there is no need for regular checkups with a technician and valves are chosen to minimize the likelihood of replacement (i.e. patient brand loyalty is minimal).

Elaborating on the ethical concerns regarding the availability of heart valves, Merryman conducted a survey about the release of a new tissue engineering technique to create heart valves for children[31]. During this exercise, bioengineer students were able to choose either an expensive and complex technique with low risks of failure or a cheap, easy technique with high risks of failure. In the end nine students voted for the expensive, low risk option and six for the cheap, high risk option. If the more expensive low risk option would be released 2.000 wealthy children would safely benefit whilst 18.000 children with lower soci-economic status would die. With the cheap high risk technique all 20.000 children would be aided but 5.000 of them would risk death due to implant failures. The aim of the exercise was to show that significantly less children would die if the second option was chosen but bioengineer students are biased towards the most safe and optimal choice even if this is the most expensive one and reduces availability of the device to less wealthy patients. Bioengineer students will be the future manufacturers deciding which medical devices will be released. Hopefully they will consider the availability of devices for patients with lower socio-economic status and the ethical implications of withholding these devices. This shows that ethical discussions related to availability still need to be held across a broad platform and are becoming increasingly more relevant with the rising demand of heart valve prosthetics.

Bioprosthetic heart valve

Since the 1960's heart valves from pigs and valves made from cow pericardium have been transplanted to humans[32]. For these bioprosthetic heart valves lifelong anticoagulant therapy is not needed because there is no increased risk of thromboembolism. When a patient receives a mechanical heart valve at the age of 25 they have a 99% cumulative chance to have had either a bleeding or thrombotic incident by the age of 75[33,34]. Thus a bioprosthetic heart valve was thought to be the ideal transplant for young patients. However for patients < 35 almost all bioprosthetic heart valves fail within 5 years, whilst the failure rate for patients > 65 is less than 10% after 10 years[33,34]. This is probably due to the immune competence of younger patients which lead to calcification of the heart valve[34]. In addition, repeated open heart surgery is associated with increased risks[34], therefore doctors tend to opt for a mechanical heart valve for younger patients, leaving both young adults and children without considerable treatment options. Regarding bioprosthetic heart valves, recently no substantial improvements have been made. With further research into xenotransplantation the improvement of the bioprosthetic heart valves seems to gain momentum again.

Xenotransplantation refers to either 1) the transplantation of nonhuman animal cells, tissues and/or organs into a human recipient or to 2) human body fluids, cells, tissues and/or organs that have had ex vivo contact with live nonhuman animal cells, tissues and/or organs[35]. Research into xenotransplantation is driven by a current organ shortage which leads to ten people dying each day in the USA alone[35]. The focus lies on developing entire human organs in pigs for transplantation. Pigs need to be genetically modified to grow a human organ and for the organ to be accepted by the recipient. Advances of this technique would make it possible to grow a human heart, and therefore human heart valves which can be used for transplantation. Because the valves are human it is expected that the immune response of the recipient will be reduced compared to porcine heart valves, resulting in longer lasting bioprosthetic heart valves. A second option is that the pig will be genetically modified so that the porcine heart valves will not provoke an immune response in the recipient, for example by disabling certain porcine specific genes. Thus, perhaps it will become possible to obtain bioprosthetic heart valves with a longer lifespan when xenotransplantation trials form a success.

According to the aforementioned definition, transplanting heart valves from pigs and cows is a form of xenotransplantation. However, in the literature it is not clearly referenced as such, even though there are ample ethical discussions about xenotransplantation in general. Perhaps the transplantation of bioprosthetic heart valves is not recognized as xenotransplantation because the technique is new and pig heart valve transplantation has been around for more than 50 years. It is likely that bioprosthetic heart valves are already accepted by society in contrast to xenotransplantation of organs. Since ethical discussions regarding xenotransplantation are applicable to bioprosthetic heart valves and there are no bioprosthetic heart valve specific ethical discussions found in the literature we will focus on these discussions.

Inherent arguments: animal rights and human dignity

Inherent arguments against xenotransplantation address whether the technique itself is acceptable and mainly focuses on animal rights and human dignity. Especially relevant is the genetic modifications of animals to make it possible for human organs to grow.

Animals are recognized as creatures with inherent value, although we tend to elevate certain species above others[36]. We for example use cow and pig material for transplantation but do not use nonhuman primates for the same purpose. Some authors argue that it is easier to use cows and pigs because we already farm them for consumption[37]. Besides, we recognize more of ourselves in nonhuman primates and therefore find it harder to farm them for our personal benefit. These justifications are based on religious and metaphysical notions which consider humans to have the most inherent value.

Ravelingien and Braeckman dedicated a paper to disprove the inherent arguments against xenotransplantation[38]. They divide the arguments into three categories: integrity arguments, intrinsic value arguments and sanctity of nature arguments. The first category consists of arguments that find that the genome of an individual/species should not be edited and should remain intact for the organism to be 'whole'. Ravelingien and Braeckman counter this by addressing that the genetic alteration needed for xenotransplantation of organs are very few and that this will leave the organism's characteristics intact. Also, the genome is always subject to change, for example due to spontaneous mutations. Thus an intact genome does not signify an organism or species 'wholeness' and genome editing will not affect their integrity. The intrinsic value arguments state that animals have a value of their own and should not be used as a service to humankind. However, animals cannot have a value of their own because it is humans specifically who assign this value. According to Ravelingien and Braeckman the notion is meaningless and superfluous. They argue that we should be able to take moral responsibility without the need of assigning intrinsic value. They also argue that if we consider intrinsic value it cannot be affected by editing the genome because this would be the same as saying that someone with an artificial limb has lost some of his or her intrinsic worth. The last category questions the technological interference with the natural order. These arguments are based on the idea that we should not manipulate the processes of life, i.e. playing God, because this defies the natural order/divine creation. Ravelingien and Braeckman explain that these arguments assume that editing of the genome is unnatural. However gene editing happens without the intervention of humans, e.g. bacteria can inject pieces of their genome into other organisms. Thus genetic alterations are a natural phenomenon. If we consider this to be different for humans than for bacteria then we distinguish nature from culture and should also object to applied farming methods because these alter the genome of the organisms through human intervention. Lastly, Ravelingien and Braeckman argue that attributing moral status to natural development is strange since it is a process without intent.

According to Ravelingien and Braeckman animals have no intrinsic value but this does not mean we should treat them poorly. Instead of arguing whether it is inherently wrong to use animals for human benefit we should consider their welfare more. This notion is supported by Daar and Phil[36]. Considering the inherent value of mechanical and tissue engineered heart valves is unnecessary because they are lifeless.

Consequentialist arguments: (reverse) zoonosis

Consequential arguments against xenotransplantation focus on possible consequences and costs to society. Examples are zoonosis (disease transmission from animal to human), reverse zoonosis and the slippery slope towards human enhancement[39]. In this debate also more general risks of stem cell based therapies are being considered, such as the possibility of human cells spreading to the animal's brain or the possibility of stem cells forming cancers in recipients. According to aforementioned papers these arguments remain relevant topics to discuss before and alongside further development of the xenotransplantation technique[36–38].

In 1997 it was discovered that porcine endogenous retrovirus (PERV) was capable of infecting human cells in vitro[40]. This means that it would be possible to transmit a porcine disease to humans via xenotransplantation, possibly creating a new human virus that could cause a pandemic as we have seen in both the past (influenza pandemic of 1918) and present (COVID-19 pandemic of 2019). Later research indicated that in vivo transmission of PERV is unlikely[41], and since there are few PERV genes they could be genetically altered to reduce risk even further. However, pathogens with zoonotic potential remain unknown because they have not been identified[37]. Infection of the host can also go unnoticed for several years increasing the difficulty of detecting possible zoonotic pathogens[37]. Currently it looks like zoonosis will remain a risk of xenotransplantation. The reverse can also be true, that a human pathogen is transmitted to the animal growing the human organ, although no paper addresses this. Animals cultivated for their organs are susceptible to such pathogens because these animals have similar genetic make-up, live under suboptimal circumstances and have diminished immune systems which makes this issue non-trivial.

Another consequence of xenotransplantation is the possibility of human cells manifesting in other places of the pig, for example the brain or gonads. This phenomenon is referred to as humanizing the pig[39]. Humanized pigs can perhaps gain human-like cognitive abilities which make them more similar to humans. This makes it harder to justify using these pigs for human benefit. According to Loike and Kadish we should not use the term humanized pig since a pig with enhanced cognitive state is still not a human and this terminology will only scare people[39]. Loike and Kadish argue that there is a difference between human cognition and personhood and that these terms should not be mixed in ethical debates[39]. They do agree that more research is needed to establish whether human cells can enhance animal cognition. Only when we understand enhanced cognition can we determine what human cognition is exactly and whether the benefits of xenotransplantation overtake these ethical concerns.

Another general objection towards xenotransplantation is the slippery slope argument[39]. Here, the argument is put forward that with the genetic modifications of animals for human health gain we get a step closer to editing the human genome to remove genetic diseases and defects, ultimately proceeding towards the possibility of a designer baby. Couples can already let their embryos be screened for genetic diseases when it is known, due to their family history, that they have increased chances of certain diseases. It is befitting to assume that a next step will be to eradicate hereditary diseases with a targetable genetic origin once we can apply this technique successfully in animals. The slippery slope argument is weak because if we would take it into account no progress would be possible. Besides, taking one step towards a goal (genetic modification of the pig for xenotransplantation) does not mean

that we will reach a possible subsequent goal (designer babies). Overtime we have seen that new techniques get accepted by society even though they were received with apprehension, this has for example been the case with preimplantation genetic diagnosis and in-vitro fertilization. Thus it seems like we are suspicious of further technical developments but get used to them over time. For example in 1996 half of Swedish respondents did not find xenotransplantation morally acceptable[42] whereas this number was reduced to ⅓ in 2003[43].

The final objection to xenotransplantation is that implanted stem cells can form cancers[39]. It has been shown in animal studies that both transplanted embryonic stem cells and induced pluripotent stem cells can form teratomas and genetic instability, leading to cancer. However, as of yet xenotransplantation aims to transplant entire organs or grafts and not stem cells thus this objection seems unfounded for current xenotransplantation application in humans. The argument is applicable to animals since they do receive stem cells to be able to grow a human organ. It is unlikely that this argument will hold ground since there is a multitude of studies that create cancers on purpose in model organisms in order to study them[44].

The inherent and consequential arguments discussed mostly focused on entire human organ transplantation using pigs, and the genetic modifications needed for xenotransplantation success. This discussion is relevant for bioprosthetic heart valves because the logical next step in their development is to genetically modify the animal host. Either to reduce the immune response of the recipient of the animal heart valve (e.g. deactivate PERV genes in pigs) or by making the animal able to grow a human organ for transplantation. This discussion is not applicable to mechanical heart valves and did not even arise with the start of bioprosthetic valve transplantation but only when complete organ xenotransplantation seemed to become a reality. Zoonosis and possible humanization of donor animals are not relevant to tissue-engineered heart valves because these prosthetics are based on an entirely different technique than xenotransplantation. However, both the slippery slope and the stem cell argument can be applied to regenerative tissue-engineered heart valves. The creation of tissue-engineered heart valves can include the use of stem cells[45] which means that it should be made highly unlikely that these cells will contribute to cancer formation. For example by transplanting only tissue-engineered scaffolds with differentiated or dead cells.
The slippery slope argument can be applied to all scientific progress and should be considered to help form an opinion regarding novel techniques but it should not stand in the way of further scientific developments.

Clinical trials

As we have seen with the Bjork Shiley valve, it used to be possible to bring a medical device onto the market without proper clinical testing. This resulted in retraction of the Bjork Shiley valve and the onset of new, more strict guidelines. Nowadays, medical devices go through thorough clinical test phases before they are made available to the wider public, although shortcomings remain. Especially since guidelines are lacking for newly developed techniques such as xenotransplantation and tissue engineering.

For pre-clinical research, cells and model organisms, such as mice, pose sufficient methods to inquire about treatment effects.The next logical step is to use model organisms that are phylogenetically closer to humans. Nonhuman primates have survived beyond six months

after receiving a pig heart xenograft upon which the experiment was chosen to be terminated[46]. This reaction will still differ from the reaction of a human receiving a pig heart xenotransplantation. Thus even after this initial success clinical trials need to be reconsidered to include human participants to learn about the physiological interaction between the xenograft and recipient. Current guidelines are not optimized to include human test subjects. Questions arise, such as: when is the clinical trial safe enough for humans to participate, what is a suitable control group and who can participate in the trial first?

Ravelingien et al. propose to first experiment on vegetative bodies before transplanting to patients[2]. These bodies have permanently lost all functioning of the cerebral cortex but have a (partly) functioning brain stem, which means that they are not aware but still perform physiologic features. In October 2021 a genetically modified pig kidney was transplanted to a vegetative body with kidney failure[47]. The experiment is considered a breakthrough: the kidney was not rejected and urine production continued as expected within the 52 hour duration of the experiment. This shows that Ravelingien et al. correctly foresaw the need of human participants in clinical trials and that the ethical discussion is still relevant today[2]. Ravelingien et al. stress that former consent is necessary to ensure that the experiment is not against the person's wishes[2]. They do not suggest a consecutive kind of participant for the continuation of the human clinical trials. Perhaps Pierson et al. make the most convincing case: they suggest patients with congenital heart disease, especially when they are unfit for a ventricular assist device or are unlikely to receive an allograft (e.g. due to high amount of reactive antibodies)[48]. These patients will likely not miss a better treatment opportunity later in their life and could perhaps even get aid from a xenotransplant when nothing else could.

Once xenotransplantation trials in humans are deemed a success, heart valves can be obtained in this manner. Tissue engineered heart valves are still in their infancy and will need to undergo a similar route of identifying the most suitable way of properly testing them in clinical trials with human participants. With current xenotransplantation success stories in nonhuman primates and vegetative bodies it seems likely that tissue engineered devices will be tested in a similar way.

Discussion

With the development of new types of heart valve prosthetics new ethical discussions have emerged and previous discussions have ceased to be relevant. Whilst discussing ethical considerations, relating to either specific types of heart valves or more general medical devices, feedback has been provided to which extent these discussions are applicable to all three types of heart valve prosthetics. Here we will discuss and recap some of the most notable findings.

With the warfarin case we have seen that patients can lack information and education about their heart valves[13] and that this phenomenon is also observed with other medical devices such as CIEDs[16]. We encountered no ethical discussions of misinformation with bioprosthetic and tissue engineered heart valves which indicates that the necessary steps have been undertaken to reduce patient misinformation. It is likely that informed consent has become increasingly important over the years and we have learnt from past mistakes. The lack of patient education of the warfarin anticoagulant therapy remains. Thus even though we observe an improvement of patient education regarding novel types of heart valves we still need to take action to provide better patient education when we observe lack of patient knowledge.

This increased awareness of needing to enable patients to make an informed decision is reflected in the increasing complexity of clinical trials. We seem to value the safety of medical devices and treatments more than we used to. Guidelines have been established or improved[20], again due to lessons learned in the past, for example the Bjork Shiley heart valve. This leads to the predicament when good is good enough[27]? On the one hand we do not want patients to suffer from medical device malfunction which could have been identified and fixed during clinical testing. On the other hand we do not want to deny patients a medical treatment which can alleviate their suffering. With current guidelines creating medical devices with newly developed techniques can be cumbersome. Already in 2004 Ravelingien et al. suggested the use of vegetative bodies for xenotransplantation[2] whilst we have only applied this suggestion in 2021[47]. This shows that it can take a long time to get a treatment from bench to bedside. This will likely be similar for the development of regenerative tissue-engineered heart valves whilst worldwide demand for heart valve transplantation remains ever increasing. We should be aware of this consideration of safety versus risk, and maybe reconsider whether the improved guidelines are not prohibiting further medical advances.

Relating to this discussion is the retraction of the Bjork Shiley heart valve. According to Fielder it was an ethically justified decision to retract the device from the market due to the misleading information provided by Shiley Inc[21]. However, mechanical heart valves are still relevant as prosthetics today and the Bjork Shiley valve was one of the best mechanical valves available[21]. Can past unethical behavior not be overlooked when the device could nowadays save and aid thousands of lives? The Bjork Shiley valve could be subjected to clinical trials before being able to re-enter the commercial market. The current improved guidelines would prevent Shiley Inc. from repeating their past mistakes. If the valves are deemed safe enough for commercial application they could help out numerous patients. In the meantime, Shiley Inc. has been taken over by the large pharmaceutical Pfizer. This means that remarketing the Bjork Shiley valve would not lead to profit for the company that

was responsible for the unethical marketing of the Bjork Shiley valve. We conclude that it is more desirable to remarket the Bjork Shiley valve than withholding it due to past mistakes.

In short, we expect that similar scenarios as the warfarin and Bjork Shiley case will not be repeated with the development of new types of heart valve prosthetics due to the implementation of stricter measurements. We do stress that we should be aware of possible adverse effects of these measurements and need to keep discussing their pro's and con's at all times to ensure that we can offer the most optimal treatment.

We see a clear separation between the origin of mechanical and bioprosthetic heart valve discussions. The former are based on specific cases whereas bioprosthetic valve discussions raise more general ethical considerations. Here we have built on the warfarin and Bjork Shiley case because they were the most prominent ethical discussions in the reviewed literature focussing on mechanical heart valves. We aimed to discuss heart valve specific ethical considerations and when these were lacking we applied more general ethical debates to heart valve prosthetics, as was the case with xenotransplantation and bioprosthetic heart valves. Unfortunately not all general ethical discussions could be covered in the span of this report. Relevant discussions that were not included are embodiment of prosthetics[49], ownership of prosthetics[49] and human enhancement[50,51] (see accompanying references for literature discussing these matters). These topics of discussions should be taken into consideration with further development of tissue-engineered heart valves but were omitted here because they were not frequently mentioned in accordance with heart valve prosthetics.

Interestingly, we found that bioprosthetic heart valves are not clearly recognized as xenotransplants even though they fit the definition of xenotransplantation[35]. Bioprosthetic heart valves are decellularized before they are being transplanted, meaning that they do not contain live cells, which makes them similar to current tissue-engineered prosthetics. According to a recent publication these porcine heart valves can also be categorized as scaffolds for *in situ* tissue engineering[52]. However, because bioprosthetic valves originate from animals it is most sensible to categorize them as xenotransplants[52]. Xenotransplantation of genetically modified heart valves can include live cells, which distinguishes these types of heart valves from current bioprosthetic heart valves[52]. Thus even though it is logical to categorize bioprosthetic heart valves and genetically modified heart valves as a form of xenotransplantation the fact remains that they differ based on the presence of live cells. Godehardt and Tönjes argue that they should therefore be regulated differently[52]. This difference in cell viability can be a reason why xenotransplantation of bioprosthetic heart valves has not raised ethical discussions like xenotransplantation of organs has.

One last consideration regarding xenotransplantation of bioprosthetic heart valves is the current COVID-19 pandemic. Even though it has been established that the chance of zoonosis via xenotransplantation is improbable it will never be zero[41]. The current pandemic can shift the public opinion from general acceptance of the technique towards more caution, thereby withholding or slowing further development of xenotransplantation and therefore its progression towards commercial availability. This shows that even with carefully established guidelines and thorough clinical trials medical devices remain subject to their timing and societal context.

We have seen that different ethical discussions regarding heart valve prosthetics have emerged and ceased to be relevant. Some of these discussions could be applied to multiple types of heart valves whereas others remained valve specific. Despite remaining ethical dilemmas there is mostly societal support for currently available heart valve prosthetics and this will hopefully continue for newly developed heart valves such as regenerative tissue-engineered heart valves. With further heart valve prosthetic development we expect to not only resolve current donor shortages but also create more suitable treatment options for patients that currently have no proper options available to them, such as children and young adults.

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