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The Risk in Avoiding Risk: Optimizing Decision Making in Structural Heart Disease Interventions

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ABSTRACT

Due to public audit of operative mortality after cardiac surgery, surgeons tend to avoid procedures with high early mortality risk. However there may be considerable risks in avoiding this risk. Careful balancing of therapeutic options from both the *clinical* perspective, the *patient* perspective, and from *societal* perspective, including taking the long view on outcome, is essential for optimal tailoring of treatment to the individual patient in current clinical practice. Illustrated by three structural heart disease cases, all three perspectives are discussed in this paper. From a *clinical* perspective, the risk in avoiding risk may be minimized by developing and using novel prognostic models that are able to simultaneously combine several longitudinally collected data during patient follow-up with these patients' outcome. From a *patient* perspective, the implementation of patient information portals and decision aids, to support shared decision making, will empower and serve the individual patient in balancing risks and benefits. From a *societal* perspective, there might be a risk in avoiding risk by reimbursing interventions with a small decrease in risk associated with high costs, causing limited access to other healthcare interventions with higher health gains using the same amount of resources. Policy makers should therefore inform their funding decisions based on cost-effectiveness analyses. The tools described in this paper—reliable prognostic models for clinicians, decision aids for patients, and cost-effectiveness models for health care decision makers—will help to find an optimal balance in 21st century structural heart disease treatment decision making from *all* perspectives.

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KEYWORDS Clinical decision making; cost-effectiveness; heart valve disease; patient preferences

Introduction

In their 2011 *British Medical Journal* paper Tom Treasure and colleagues asked the cardiovascular community the question "Is there a risk in avoiding risk?"[1] This question related to their observation that due to public audit of operative mortality after cardiac surgery, surgeons tend to avoid procedures with high early mortality risks. By focusing on early outcome, the long-term perspective for the patient may not always be optimally served. With their landmark paper they addressed a delicate issue in 21st century cardiovascular interventional practice, namely the dire need for a broader view on balancing of risks and benefits of different treatment options.

Careful balancing of therapeutic options from both the *clinical perspective*, the *patient perspective*, and from *societal perspective*, including taking the long view on outcome, is essential for optimal tailoring of treatment to the individual patient in current clinical practice. Illustrated by three structural heart disease cases, all three perspectives will be discussed in this paper.

Discussion

Case 1: The clinical perspective: balancing risks and timing of (re-)interventions

A 35-year-old male patient presents with progressive fatigue and symptoms of palpitations. He was diagnosed with tetralogy of Fallot at birth and underwent primary repair at the age of 3 with the RVOT being reconstructed using a transannular pericardial patch. Current echocardiographic examination shows moderate pulmonary regurgitation.

The clinical challenge in this patient is to predict the optimal timing of reoperation and reconstruction of RVOT with, usually, an allograft. At this time there is no evidence-based consensus on optimal timing for RVOT reconstruction while the prevalence of adults with congenital heart disease increases at a rate of 5% per year. The risk in taking the risk of early surgery in patients with mild symptoms is that it can lead to more reinterventions during a patient's life than strictly necessary. On the other hand the risk in avoiding risk by delaying surgery in such patients increases the risk of irreversible right ventricular (RV) dysfunction, RV failure

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and eventually death. It is important to take into account that most patients who need an RVOT reconstruction are young and therefore likely to require further surgery as prostheses have a limited lifespan. Carefully determining the optimal timing of surgery can significantly reduce the number of reinterventions in these patients during their lifetime while minimizing the risk of irreversible RV dysfunction.

This example illustrates the need for reliable prognostic models that help clinicians to determine the optimal timing of (re-)intervention.

Although therapeutic and etiological research receives most attention in healthcare, prognostic research is evenly important when it comes to patient treatment. The aim of prognostic research is estimating the magnitude of risk in individual patients over a certain time period. This risk can include specific outcomes such as death, reoperation, stroke, but also outcome measurements such as quality of life impairment. Individual patient prognosis depends on patient (e.g. age, gender, comorbidities) and procedural characteristics. In order to be able to predict patient prognosis, prognostic models are needed. These models can combine several patient and procedural characteristics to estimate the risk of a future outcome for the patients. Another important aspect of prognostic models is that they help to identify those patients that can benefit most from a particular treatment. Prognostic models can be used to estimate outcome on different levels: individual patient level, specific group of patients level and complete series level. Most current prognostic models perform reasonably well on the level of complete series. However, their performance is far from optimal in the first two levels.

During the last decades at least 20 risk prediction models have been developed for patients in need of cardiac surgery, such as the European System for Cardiac Operative Risk Evaluation (EuroSCORE 1 and 2) and the Society of Thoracic Surgeons (STS). However, none of these models is able to accurately predict the outcome of the individual patient after cardiac surgery.[2] From a clinical point of view, several reasons exist for the inadequate performance of currently available models. First of all, most models are developed using historical data and with continuous change in patient population over time these models can quickly become outdated. Furthermore, data used for the development of prognostic models is usually from a very heterogeneous patient population, making the model less accurate for certain subgroups of patients. In addition, the association between potential prognostic factors used for model building and patient outcome may also gradually change over time. From a statistical point of view, two important reasons exist for the inadequate performance of currently used prognostic models. The first is that these models do not adequately correlate the *longitudinal data* that are collected during follow-up of patients (e.g. biomarkers, echocardiographic data, ECGs) with these patients' *clinical outcomes* (e.g. valve failure, reoperation, death). The second important reason for inadequate performance of current prognostic models is that they are all *static*, which means that once they are built they are no longer updated in the future while patient populations are continuously changing and new treatment options become available. All these shortcoming have a major influence on these models' discrimination and calibration capabilities. Furthermore, surgeons and other healthcare providers are usually interested in what the short-term result of the medical intervention is while the long-term outcome is of more importance to individual patients. Therefore, ideally the starting point of scientific research should not be the procedure, but the individual patient and the end point the prospect of their future life. For example, there is no single 'best choice' in selecting a prosthetic valve for an individual patient since all these factors can be valued differently by individual patients. A patient may very well prefer a higher operation risk (e.g. the Ross procedure vs. a mechanical valve) or a 60% life-time risk of reoperation with a bioprosthesis over a 20% life-time risk of a major TE or bleeding with a mechanical valve, or vice versa, depending on his or her preferences. This may result in taking a greater risk in the short term if the consequence is a larger potential benefit for the patient in the long term (in terms of survival and/or quality of life). In this regard, another major disadvantage of current prognostic models is that they put too much emphasis on early mortality and ignore other aspects of outcome such as long-term morbidity and mortality, and quality of life. It may cause decreased access to surgery/intervention for those who might benefit most. This *risk in avoiding risk* may be minimized by developing and using novel prognostic models that are able to simultaneously combine several longitudinally collected data during patient follow-up with these patients' outcome, as detailed below. These models do not only predict patient mortality but also patients' quality of life and disease burden (e.g. number of reoperations).This approach is called joint-modeling and enables us to investigate, for example in our 35-year-old patient, to what degree serial echocardiographic measurements (or certain biomarkers) are capable of predicting events (e.g. death or reoperation) that patients might experience after a certain treatment.[3–5]

The *first step* in creating a joint model is analyzing repeatedly collected data with longitudinal models. Several methods for longitudinal analyses exist. Both linear and non-linear structures can be used to analyze longitudinal data. In linear methods, the degree of the outcome (y) is determined by the degree of the input (x), which can be written as a $y = ax+b$ equation. An important characteristic of linear methods is proportionality since there is a straight-line relationship between the input value and the outcome. Therefore, the behavior of linear methods can be fully predicted. In non-linear methods, the model uses parameters that are allowed to vary. Therefore, the assumption of proportionality is absent in non-linear models and the behavior of such models cannot be fully predicted. The cardiovascular system is a complex mechanical, chemical, and hemodynamic system in which the processes are often related via a variety of mechanisms. Therefore, these processes are often non-linearly structured.[6–8] Since the principle of proportionality may not be valid, using linear methods may result in simplification of the real process and, therefore, inaccurate results and inferences. On the other hand, the application of non-linear models is relatively time-consuming and requires advanced biostatistical expertise. The 2008 guidelines for reporting mortality and morbidity after cardiac valvular

interventions[9] propose the use of longitudinal data analysis for series of assessments like repeated echocardiographic measurements of valve function to estimate its average temporal pattern and variability in a group of patients. These methods enable the researchers to model the trend of various repeatedly collected data such as echocardiographic measurements over time after allograft implantation. Using these methods it is possible to visualize the temporal trend of, for example, each aortic regurgitation grade over time during follow up. Clinicians can use such temporal trends to determine on average how for example aortic regurgitation develops over time after aortic allograft implantation. From a statistical perspective, these types of methods are superior and more informative compared to the methods where repeated outcomes are dichotomized and inadequately analyzed with actuarial methods as if they were events, such as freedom from grade 1+ or 3+ aortic regurgitation after aortic valve surgery.[10,11] Assessing the trend of longitudinal outcomes of interest and identifying factors that influence these outcomes over time can be of particular importance since it can help the clinicians understand how a certain process changes over time and thus can contribute to a better patient management (e.g. by determining which patients should be monitored more closely by their physicians and at which time interval). The *second step* in creating a joint-model is combining the longitudinal analyses of repeated measurements with the events that the patient may experience during follow-up. In joint-modeling, typically a mixed-effects model is used for the longitudinal data and a Cox model for the survival data in order to build a single model where dependency and association between these types of data is taken into account.[12] This approach can ultimately lead to a less biased and more efficient identification of potential prognostic factors of a certain outcome.[12] The joint-model can be constructed in a way so that it becomes dynamic which means that the prediction model will take into account time-dependent changes in patient population, risk factors, improvement in surgical techniques and improvements in the quality of pre-, peri- and postoperative patient care. The problem with the application of joint modeling is currently the complexity of the analyses and lack of appropriate software. It can be expected, however, that these issues will become less important when freely available and easy applicable software that supports physicians to translate risks and benefits to their patients in an understandable manner, will become more readily available in the near future.

Case 2: The patient perspective: balancing risks, benefits and patient values

A 55-year-old female presents with fatigue and dyspnea on exertion. Echocardiographic examination reveals a bicuspid aortic valve, severe aortic regurgitation with normal annular and aortic root dimensions and a dilated LV.

The clinical challenge in this patient is in the appropriate selection of a surgical strategy to repair or replace the diseased valve, taking into account the risk and benefits of the different therapeutic options in relation to patient values and goals in life.

Therapeutic options for this patient include mechanical or bioprosthetic valve replacement, aortic valve repair, and some may argue the Ross operation. Since there are no perfect heart valve replacement options, as all surgical options carry substantial disadvantages, operated patients will either face the burden of mechanical valve implantation (anticoagulation-related and valve sound) or biological valve implantation/repair (limited durability). In addition the option of aortic valve repair and the Ross operation is restricted to a limited number of centers of expertise.The risks in risk avoidance in this clinical challenge are twofold: first of all surgeons may not want to take the (perceived) increased risk of early technical failure in valve repair or early mortality in the Ross operation and choose for a standard mechanical or bioprosthetic valve replacement thereby ignoring the long-term perspective for the patient that may be better served with valve repair or a Ross operation. Secondly, surgeons may very well prefer to implant a mechanical prosthesis to avoid having to perform a reoperation in a 55-year-old patient who is likely to require a reintervention in the next 15–20 years, exposing the patient to the burden of anticoagulation and valve sound. In addition, patients who are usually not knowledgeable and rely heavily on their physician in decision making may not be able to weigh the options in their own context and take both short- and long-term perspective into account.

In particular, younger adult prosthetic valve recipients face considerable lifetime risks of valve-related complications. Besides balancing the magnitude of these risks in selecting a heart valve prosthesis, there is also the need to balance patient values in relation to these risks. For example: one person may prefer a 100% lifetime risk of a reoperation on a biological valve over a 20% lifetime risk of a major bleeding with a mechanical valve, while others prefer the opposite, driven by their lifestyle, values, and preferences. Also, in some circumstances a patient may be willing to trade in quantity of life for a better quality of life, or vice versa.

Aicher and collegaues studied in a non-randomized setting quality of life and anxiety and depression after mechanical valve implantation, the Ross procedure, and aortic valve repair, and found that quality of life, including valve-related aspects such as bothersome valve sounds, frequency of medical visits, and fear of potential complications such as bleeding or reoperation for valve failure, is influenced by the type of operation.[13] Several other authors have reported comparable observations. It is therefore not surprising that there is increasing recognition of the necessity to address patient preferences in prosthetic heart valve selection, and both the ESC/EACTS and AHA/ACC VHD guidelines have implemented this in their recommendations, advocating a shared decision-making process in prosthetic heart valve selection (Class I, Level of Evidence C).[14,15]

The concept of shared decision making is promoted on both sides of the Atlantic: patients should be fully informed about the indications for the surgery, risks of anticoagulant therapy, and the potential need for and risk of reoperation in a shared decision-making process that accounts for the patient's values and preferences. Although both patients and clinicians find that shared decision making should be pursued we are far from optimal implementation of this concept.[16,17]

The use of patient decision aids to support the shared decision-making process may be helpful in this regard. A recent randomized trial showed that although the use of a patient decision aid to support prosthetic heart valve selection does not make valve selection less difficult, it does result in improved patient knowledge, and patients also feel better informed, less anxious and depressed, and experienced a better mental quality of life at the time of the decision making.[18] Interestingly, a randomized trial of a PCI choice decision aid for stable coronary artery disease published 2 months earlier, reported almost identical outcomes.[19] In addition, the same group studied cardiovascular clinicians' perceptions of shared decision making following use of the PCI choice decision aid and identified gaps in clinician knowledge around shared decision making, and reluctance among clinicians to modify their baseline practice, although they express their interest in using decision aids after they have been exposed to them in a research setting.[20] This suggests that the introduction of decision aids in cardiovascular clinical practice is not only effective in empowering patients, but may also help to instruct clinicians on optimal implementation of shared decision making in their clinical practice. We do need to further build frameworks for cardiovascular patient preferences in order to find out what really matters to patients with cardiovascular disease when it comes to deciding on whether or not to undergo a procedure, choosing a particular procedure, or optimally time a procedure.[21]

From a patient perspective the future of clinical decision making in structural heart disease looks promising: with increasing emphasis on patient reported outcome measures and patient reported experience measures and the implementation of patient information portals and decision aids to support shared decision making, health care is slowly transforming to optimally empower and serve the individual patient in balancing risks and benefits, both in the short and long term. It does require a different role pattern: for doctors to take a more guiding role, and for patients to be proactive and become a full member of their own heart team.

Case 3: The societal perspective: balancing risks, benefits and costs of treatment options

A 75-year-old male with a history of COPD, diabetes mellitus type 2, and castration-resistant prostate cancer presents with severe symptomatic AS. Echo-Doppler evaluation reveals normal-sized cardiac chambers, septal and posterior wall thickness of 13 mm, normal left ventricular function, calcified aortic valve with a peak trans aortic flow velocity of 4.5 m/s.

The clinical challenge in this patient is to select an appropriate strategy to treat his symptomatic AS, carefully weighing risks and benefits of the different treatment options, including informed patient preferences, while at the same time containing the costs of treatment given the short estimated life expectancy of this patient and the high costs associated with invasive treatment.

During the last few decades, health expenditures have been rising across OECD countries. For instance, in the US the health expenditures per capita have increased from $327 in 1970, to $4559 in 2000, and to $9451 in 2015.[22] More importantly, not only absolute expenditure but also the relative share of the Gross Domestic Product (GDP) spent on health has increased across OECD countries, for example in the US from 6.2% in 1970, to 12.5% in 2000, and to 16.9% in 2015.[22] This increase in health expenditures is expected to continue to rise in the coming decades, due to the ageing population but also due to technological developments.[23] Increasing health expenditures are also expected in the field of heart valve interventions. The ageing population in combination with the trend of increasing prevalence of valve disease with age will result in an increase in the number of patients requiring valve implantations.[24] Furthermore, there are many emerging technologies such as tissue-engineered heart valves and less invasive implantation methods.

As a consequence of these increasing healthcare expenditures, policymakers in all healthcare systems are faced with the challenge to keep their healthcare system financially viable in the long term while at the same time maintaining access to healthcare of good quality.[25] If resources are committed to one intervention, they are not available to fund and deliver other interventions.[25] Therefore policy makers should ask themselves whether an intervention is worth funding compared with other things they could do using the same resources.[26] The decisions of policy makers to fund one intervention carries the risk of inhibiting access to other interventions that might result in more health gains. The optimal situation from a societal perspective would be to allocate the limited resources in a way that maximizes the health of the overall population by avoiding the implementation of ineffective or comparatively inefficient interventions.[27] To achieve this, decisions about allocation of the limited resources should be informed by health technology assessment (HTA) studies. HTA is a multidisciplinary process where social, economic, organizational and ethical issues are evaluated, but the core of HTA is often the cost-effectiveness analysis.[28] Cost-effectiveness analysis seeks to identify which interventions offer health gains large enough, relative to their costs, to warrant reimbursement by the healthcare payer.[25] In a cost-effectiveness analysis two or more alternative interventions are compared in terms of their costs and health effects.[26] The main outcome of a cost-effectiveness analysis is the incremental cost-effectiveness ratio (ICER) which represents the average costs per quality adjusted life year (QALY) gained.[26] An intervention is cost-effective when the ICER is below a certain cost-effectiveness threshold, which is often set by policy makers. It is important to note that although cost-effectiveness analyses provide important information to policy makers, the efficacy, effectiveness, and availability (i.e. is the intervention reaching those who need it?) of the intervention should also be taken into account by policy makers.[26]

Considering cost-effectiveness in healthcare decision making influences the availability of transcatheter aortic valve implantation (TAVI) as a treatment option for the aforementioned patient. The cost-effectiveness of TAVI compared to currently used interventions depends on whether the high costs of the TAVI device can be offset by cost reductions of other elements of the intervention, and if not, whether the higher costs of TAVI can be justified by increased survival and/or improved quality of life.[29]

Although the costs of TAVI are substantially higher than the costs of the alternative treatment for inoperable patients (often medical treatment), most cost-effectiveness studies have shown that this is compensated with a sufficient gain in QALYs resulting in acceptable cost-effectiveness estimates (i.e. ICER).[30,31] In contrast, the cost-effectiveness of TAVI compared to surgical aortic valve replacement (SAVR) in high-risk operable patients is less straightforward. The price of the TAVI device is substantially higher than the price of surgical valve prostheses (≈$30,000 or ≈€18,000 for TAVI devices versus ≈$5000 or ≈€3000 for surgical valve prostheses [29,32]). The high TAVI device costs are partially compensated by a reduction in cost due to shorter procedure time and hospital stay, and lower use of blood products after TAVI compared to SAVR.[32–34] Despite these cost reductions, TAVI remains more expensive than SAVR.[31–34] The higher costs of TAVI compared to SAVR need to be compensated with benefits in health outcomes in order for TAVI to be cost-effective. Most cost-effectiveness studies have shown small differences in QALYs (ranging from −0.61[35] to 0.32[34] QALYs) after TAVI compared to SAVR, but the majority is in favor of TAVI.[31,33,34] These differences in estimated costs and health outcomes between studies have resulted in inconsistent cost-effectiveness estimates.[31,33,34] The large US trials and several model-based economic evaluations in other countries reported acceptable cost-effectiveness estimates,[31,33,34] while other studies report less favorable cost-effectiveness estimates of TAVI compared to SAVR.[31] For more clarity on the cost-effectiveness of TAVI versus SAVR, additional cost-effectiveness analyses using data from real world clinical practice instead of randomized clinical trials are needed.

In addition to the use of TAVI in inoperable and high-risk operable patients, the use of TAVI in intermediate-risk operable patients has been studied. Recently, two large randomized clinical trials have shown that TAVI is non-inferior to SAVR in intermediate-risk patients regarding mortality and disabling strokes.[36,37] Since there is no survival benefit, the costs of TAVI need to be lower and/or the quality of life after TAVI needs to be higher than after SAVR in order for TAVI to be cost-effective compared to SAVR in these patients. However, the reduction in costs due to the shorter length of hospital stay of approximately 3 days seems too small to offset the high TAVI device costs[36] and the quality-of-life difference in patients after TAVI compared to SAVR in intermediate-risk patients is unknown. Therefore cost-effectiveness studies estimating the exact cost difference and the survival and/or quality-of-life benefits are necessary to determine the cost-effectiveness of TAVI compared to SAVR in intermediate-risk patients.[29]

But how can these cost-effectiveness estimates implicate the access to TAVI for patients? As mentioned before, policy makers can use these estimates when deciding about spending the healthcare resources to fund TAVI. In other words, the policy makers decide whether or not the costs of TAVI will be reimbursed by the healthcare payer. The use of an intervention is heavily dependent on this reimbursement.[38] The cost-effectiveness estimates of TAVI compared to the standard treatment have resulted in the reimbursement and therefore adoption of TAVI as a treatment for inoperable patients in many countries. In contrast, there is a lot of variation in the reimbursement of TAVI in high-risk operable patients.[38] For example, TAVI is fully reimbursed in Germany, while the reimbursement of TAVI for operable patients in the UK is still under review because the evidence on the efficacy of TAVI has been found inadequate.[39] This has profound implications for the adoption of TAVI: in countries where TAVI is fully reimbursed, the number of TAVIs performed was substantially higher than in countries with constrained reimbursement of TAVI.[38] Although there may be more reasons for the lower adoption of TAVI in some countries, the questionable cost-effectiveness of TAVI versus SAVR could have influenced the policy makers' decision for constrained reimbursement of TAVI in some countries resulting in limited access to TAVI.

From an individual patient perspective, the limited access to TAVI might seem unfair, as patients might want to benefit from the minimal invasive nature of TAVI compared to SAVR. However, considering the health of the overall population, this choice can be justified since the resources that would have been spend on TAVI if policy makers had decided to fully reimburse its costs, now can be spent on other interventions that deliver more health gains using the same resources. However, this might change in the future because it is expected that, as TAVI is being performed more frequently, market forces will decrease the price of the TAVI device.[32,40] If this results in a cost reduction of the TAVI procedure that results in undoubted cost-effectiveness of TAVI versus SAVR, then the risk of foregoing health benefits due to not being able to spend the resources on other healthcare is compensated by the value for money provided by TAVI.

From an economic perspective, the answer to the question "Is there a risk in avoiding risk?" is that there might be a risk in avoiding risk by reimbursing an intervention with a small decrease in risk associated with high costs (i.e. high ICER). This risk would entail limited access to other healthcare interventions that might have provided more health gains using the same amount of resources. To avoid this risk, policy makers should inform their funding decisions with results from cost-effectiveness analyses. Ideally, this would lead to an allocation of the limited available resources that maximizes the health of the overall population.

Conclusion

From all possible perspectives—*clinical, patient,* and *societal*—there may be a risk in avoiding risk in 21st century structural heart disease treatment decision making. The tools described in this paper—reliable prognostic models for clinicians, decision aids for patients, and cost-effectiveness models for health care decision makers—will help to find an optimal balance in decision making from all perspectives. By taking this diversity of perspectives into account, including the short- and long-term perspective on outcomes, we are entering a new exciting era that moves away from "risk" management (and short-sighted risk avoidance) toward "value-driven" management of structural heart disease.

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