Safety management in mechanical heart valve replacement and oral anticoagulant therapy

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Chapter 1

Introduction

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1.1 RISK AND SAFETY IN HEALTHCARE

Healthcare is for many people a matter of course. Patients expect to be cured and consider disease an exceptional event. In contrast, also many consequences of current medicine are unwanted but unavoidable. They are accepted as complications, i.e. iatrogenic morbidity and mortality. Every medical decision is based on a balance of risks and benefits. However, it is often difficult to estimate the risks for a particular patient even when there is some knowledge of the general risks associated with a treatment. In addition, the balance of risks and benefits is different in the short and long term\(^\text{(1,2)}\). Besides, healthcare is not considered a procedural process. If danger threatens, the professional in charge feels justified in deviating from the protocol and they are free to apply unusual and unproven interventions simply with an appeal to their expert status. Personal skills, endurance and a successful record of coping well with risks prove medical mastery.

Doctors have the obligation to inform patients about all possible complications involved with a diagnostic or therapeutic intervention. However, the general public has high expectations of modern healthcare, and a lack of acceptance or understanding of the risks underlies some of the feelings of injustice experienced by patients whose disease does not respond satisfactorily to treatment or who suffer from complications. Besides, poor communication between patient and health workers aggravates the patient's and relatives' perception of injustice, this being an important contributing factor in litigation\(^3\).

It will be a difficult multidisciplinary task to find out if an adverse outcome is due to an unavoidable risk of the treatment or due to human error, shortcomings of an organisation, breakdown of equipment or a device, inferior practice or violation of protocols and accepted standards of practice. Harm to a patient may simply be a complication of treatment, but in many cases unsafe practice cannot be excluded as a contributory cause.

Bignell defines risk management as "the process of making and carrying out decisions to minimise adverse effects and accidental losses\(^4\). Making these decisions requires identification, analysis, choice, implementation, and monitoring with regard to risks". A risk and safety assessment may concern a task, procedure, or process, or may be a feature of the performance of a drug or device. When we look at an industrial (procedural) process in order to assess and manage its safety, five aspects can be taken into consideration\(^5,6\):

1. the chances of failure of the system as a whole or of its various subsystems
2. the failure modes and scenarios
3. setting a safety standard and maintaining and/or resetting norms of safety
4. the potential or real damage related to the failure
5. damage control, compensation, and preventive measures

When we talk about risk and safety management in healthcare, analysis of the adverse outcome has to be based on observations at the individual level of the patient-doctor
relationship, the organisational level dealing with the duties of institutional and professional bodies, the sector level in which the various streams of healthcare are assessed and compared, and the societal level at which policy making with respect to the funding of quality assurance of healthcare, claim behaviour of patients, and public risk perception are controlled.

The multidisciplinary approach is an upcoming perspective in medicine. For instance, when confronted with implant failure of abdominal aortic endovascular grafts, the Dutch Society of Vascular Surgery and the Association for Intervention Radiology founded a multidisciplinary working group to promote the quality of the endovascular use of endoprostheses in the treatment of abdominal aneurysms. The working group recommended the introduction of a safety committee. This committee collects information from researchers and manufacturers, helps doctors to control and solve problems, and acts as an advisor to the Health Care Inspectorate. More or less the same approach is or could be used for various other professions that use ‘critical’ products like self-test devices for patients on oral anticoagulant therapy, blood products, or breast implants. However, these initiatives require a professional demand, a vision of safety and a manual on how to do it.

1.1.1 Professional credibility and the patient-doctor contract in implant surgery.

Basically, patients and doctors have a contract in which the use of a device is incorporated. Prior to treatment the patient is informed regarding the risks of failure, which may be acceptable to him or not. So, the patient always has to accept certain risks of adverse outcome. Depending on indication, disease state, the professional standard and the technical state of the art, the patient is supposed to have accepted reasonable risks of adverse outcome including device failure. In case the expectations due to technical failure cannot be met, the patient and or his relatives are entitled to be informed about the aetiology of the failure. Whether or not a device failure is due to any negligence on the part of the surgeon or the manufacturer may be established in a legal procedure. However, violation of safety standards, lack of preimplant tests, misrepresentation of patients by promising too much and substandard manufacturing technologies provide in many law systems a basis for financial compensation. So, it is profitable to invest in safety as it adds to the credibility of surgeons and industry for using high-profile implants and it also avoids litigation\(^7\).

1.1.2 Ethical considerations

First of all, the ethical principles are plain and simple\(^8\):

1. Do not harm the patient and respect the patient's autonomy and physical and mental integrity.
2. Doctors should do the utmost for patients and should not turn down a request for help.
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3 Doctors should fully inform their patients about potential benefits and risks of harm. So, it is clear that doctors need to act as safely as possible.

However, we know that all medical decisions whether or not to intervene may result in adverse outcome. An adverse event may potentially affect the perception of good quality and safety related to that decision. Today, the most commonly used ethical perspective to justify adverse outcome is an appeal to the utility principle\(^{(9,10)}\). This principle supports the concept of exposing patients to real risks of death and disability in case the chance that the patient will benefit from the intervention outweighs the chance of negative outcome. On the level of groups of patients this means that the vast majority of the group will benefit and only a minority will not. Withholding the treatment to the whole group will cause all patients to die. In the worst-case application, this principle justifies the use of potentially lifesaving interventions at very high risks of mortality, when a wait-and-see approach will certainly result in death in the very short term. The utility principle rules medical decision making in cardiac surgery. In the extreme spectrum of this perspective, only relevant damage due to the lack of safety will be taken into consideration, when looking at heart valve treatment.

The balancing of risks and benefits may be tested from the perspective of the deontology principle\(^{(9,10)}\). This principle encourages that each individual must be given the right to make his own decisions and that individual rights must be a priori respected and protected. Unwanted restriction of these rights and damage due to such restrictions should be compensated. In malpractice claims, testing of the reasonability of the risk-benefit considerations and the respect for the patient's rights are operationalized. A third test perspective is found in the cost-effectiveness paradigm on which the assignment of scarce resources is justified. So wasting resources on avoidable losses due to the lack of reasonable safety measures, will affect the justification of a treatment.

1.2 RISK AND SAFETY IN HEART VALVE REPLACEMENT

Since the development of the heart-lung machine in the fifties and early sixties of the 20th century open-heart surgery became a large-scale surgical procedure. Failing native heart valves, which may cause regurgitation or a high-pressure gradient over the valve due to stenosis, represents many of the heart diseases. Causes of diseased heart valves are infection, rheumatic fever, degeneration and congenital malformation. In many cases valve replacement by means of a mechanical valve is the common mode of treatment. An alternative is the use of a cadaver valve or a valve composed of biological material, which have a limited durability or availability. The advantages of mechanical heart valves are custom ready availability and a lifelong durability. The disadvantage of treatment with a mechanical valve is lifelong need for anticoagulant therapy.
1.2.1 Mechanical heart valves

The first mechanical heart valve prosthesis ever used was the Starr-Edward cage ball valve in the early sixties. The development of many other valves followed (the Medtronic-Hall monoleaflet, the Edwards-Duromedics bileaflet, the St Jude Medical bileaflet and the Björk-Shiley tilting disk). However, especially during the first decade of mechanical heart valve implantation, many valves were hampered by mechanical failure\(^{(11-14)}\). Examples of valve failure are metallurgical fatigue, cracks, and fracture of the welded outlet strut, finally leading to disk escape, leaflet fracture, increased wear, due to design and flaws in the pyrolytic carbon coating and impingement\(^{(11-17)}\). Other complications of valve replacement therapy, not directly affecting the valve's structural function, are paravalvular leakage and endocarditis. Many studies were executed to improve the design of the valve and to decrease the risk of valve-related complications. This thesis will go in detail into the cases of valve failure, risk and safety assessment of valves and the possible measures to take.

1.2.2 Thromboembolic and bleeding complications in patients with mechanical heart valves

Despite ongoing developments in material and design, one of the most frequent complications in patients with a mechanical heart valve prosthesis is the occurrence of valve-related thrombosis\(^{(18)}\). The increased tendency of blood clot formation around the artificial surface of the valve can prevent it from opening or closing properly. Particles of the clot can migrate and these emboli may cause damage to the brain (cerebrovascular infarction or stroke) or other parts of the body. Furthermore, a thrombotic coating on the valve can be a breeding ground for bacteria, ultimately resulting in a bacterial infection of the inner layer of the heart (endocarditis). Hence, artificial heart valve-associated blood clot formation contributes considerably to long-term morbidity and mortality in patients that have received a mechanical heart valve prosthesis. Oral anticoagulants (vitamin K antagonists) have been in use for years as an effective modality for the prevention and treatment of these thromboembolic events. However, anticoagulation is associated with another potentially fatal complication: bleeding. The treatment constitutes a delicate balance between the two complications.

Factors determining the risk for thromboembolic complications are partly dependent on concomitant risk factors for thromboembolism in a particular patient, such as the presence of atrial fibrillation, but also on properties of the prosthetic valve itself, such as flow characteristics, valve design and use of modern biomaterials\(^{(18)}\). These valve-dependent factors have been improved over recent years. However, a considerable risk of systemic thromboembolism still remains, for the prevention of which anticoagulant treatment is mandatory.
With modern valve prostheses, most important factors that may determine the risk for the development of thromboembolic complications are the position of the valve (i.e. the aortic position as compared to the mitral position), the number of artificial valves in a patient, and the type of artificial heart valve\textsuperscript{(18,19)}. A patient with a St. Jude (bileaflet) valve in the aortic position, who is not using any anticoagulant agent has a risk of thromboembolic complications of 12.3%/year, whereas the presence of a St. Jude valve in the mitral position is associated with a risk of 22.2%/year\textsuperscript{(20-22)}. The presence of more than one artificial valve further increases the thromboembolic risk. Observations in patients who were not using anticoagulant agents revealed an incidence of thromboembolic complications of 91%/year with a St. Jude valve prosthesis in both the aortic and the mitral position. Differences between types of artificial valves are illustrated by the observation that in patients who are not anticoagulated, the risk of thromboembolic complications with a Björk-Shiley (spherical disk) prosthesis in the aortic position is 23.0%/year, as compared to the 12.3%/year for a St. Jude valve in the aortic position\textsuperscript{(23)}. The use of caged-ball valves is associated with even higher incidences of thromboembolic complications.

1.3 THE COMPLEXITY OF ANTICOAGULANT THERAPY

1.3.1 Anticoagulant therapy in patients with a mechanical heart valve

The early evidence that oral anticoagulants are required for the treatment of patients with mechanical prosthetic valves came from observational studies that the high risk of systemic arterial embolism in untreated patients was reduced by anticoagulant therapy. For ethical reasons, clinical trials directly comparing oral anticoagulants with an untreated control group in patients with prosthetic heart valves have never been performed. However, randomised trials comparing oral anticoagulants with antiplatelet treatment in the prevention of thromboembolism in patients with prosthetic heart valves have clearly shown the superior efficacy of coumadins or warfarin\textsuperscript{(19,21)}. Most studies show that treatment with antiplatelet agents alone for the prevention of thromboembolic complications in patients with prosthetic heart valves is not as effective as treatment with oral anticoagulant agents. A number of studies have focussed on the issue whether the addition of antiplatelet agents to oral anticoagulant treatment in patients with a higher risk of thromboembolism would further decrease the incidence of this complication\textsuperscript{(24)}. Aspirin in doses of 500 mg in combination with oral anticoagulants was more effective than anticoagulant treatment alone in reducing thromboembolic complications of prosthetic heart valves. However, the combination of oral anticoagulants and aspirin considerably increased the incidence of serious gastro-intestinal bleeding. Recent studies indicated that the use of low dose aspirin (100 mg daily) in
conjunction with oral anticoagulant agents significantly reduced the mortality, vascular mortality and major embolism in patients with mechanical heart valves with only a minor and acceptable increase in the incidence of hemorrhage\(^{(24)}\). Some studies have suggested that dipyridamole is effective in reducing valve-related thromboembolism when administered in combination with oral anticoagulants but these findings have been challenged.

The beneficial effect of the anticoagulant treatment may (partly) be offset by the increased risk on (major) bleeding associated with the use of oral anticoagulant therapy. Therefore, several studies have addressed the issue of the optimal intensity of the anticoagulant treatment in patients with prosthetic heart valves. Accumulated results of these studies indicated that a therapeutic target INR of 2.5-4.9 was associated with a minimal risk on thromboembolic complications of 1.6%/year with a hemorrhagic event rate of 1.2%/year. A lower intensity of anticoagulant treatment, i.e. an INR in between 1.6 and 1.9, was associated with a higher thromboembolic complication rate (2.7%/year) and a slightly lower hemorrhagic event rate (0.7%/year), whereas higher treatment intensities (INR 4.9-7.4) resulted in a higher incidence of hemorrhagic events (1.7%/year) without a decrease in the thromboembolism rate (2.2%/year) as compared with the target INR of 2.5-3.0\(^{(19,25)}\).

An evaluation of anticoagulant therapy in 1608 patients with mechanical heart valves with a mean patient follow up of 4 years showed a thromboembolic complication rate of 0.7%/year, whereas the incidence of hemorrhagic events was 2.68%/year (CNS hemorrhage 0.57%/year and major extracranial bleeding 2.11%/year)\(^{(26)}\). Analysis of these data revealed an optimal intensity of oral anticoagulant therapy (defined as the INR range at which the combined incidence of thromboembolic complications and major bleeding complications was lowest) of 2.5-4.9, at which intensity the incidence of all adverse events (major thromboembolism, major bleeding and unclassified stroke) was 2.0%/year. In conclusion, to date the optimal intensity of anticoagulant treatment in patients with mechanical heart valves is aimed at an INR of 2.5-4.9. To achieve this, a target INR of 3.0 to 4.0 is recommended.

Efforts have been made to come to a more refined assessment of the optimal level of INR in patients with mechanical prosthetic heart valves dependent on the position and the type of valve. Analysis of subgroups of patients revealed that within the optimal INR range differences in the incidence of thromboembolic complications still exist. The incidence of thromboembolism was 0.5%/year with a prosthetic heart valve in the aortic position, 0.9%/year with a prosthetic mitral valve and 1.2%/year for both aortic and mitral valves. Thromboembolic complications occurred in 0.5%/year of patients with bileaflet valves, in 0.7%/year of patients with a tilting disk valve and in 2.5%/year in patients with caged ball or caged disk valves. Also, thromboembolic events were more frequent in patients 50 year of age or older, whereas bleeding complications occurred preferentially in patients older than 70 year\(^{(19,6)}\). There is, however, insufficient data to definitively address the issue which subgroup of patient should receive anticoagulants at which intensity. Trends suggest that an INR of 2.0
to 2.9 might be more effective and safe in patients with bileaflet valves, whereas patients with tilting disk valves had lowest adverse events rates in the INR range of 3.0 to 3.9. Trends in patients with caged ball or caged disk valves showed the lowest incidence of adverse events at an INR of 4.0 to 4.9.

1.3.2 Management of anticoagulant therapy

The adequate control of anticoagulation is of utmost importance in the prevention of unwanted clinical outcome in patients with mechanical heart valves. Regular control of the intensity of anticoagulant treatment by means of the prothrombin time (PT) is therefore indicated. Unfortunately, due to the variability of the dose-response of coumarin derivatives, maintaining the intensity of anticoagulation in the appropriate therapeutic range is difficult, necessitating frequent laboratory control and dose-adjustments.

The monitoring of the anticoagulant status by means of the prothrombin time (PT) and the advise to dosage the therapy by means of coumarin derivatives is usually carried out by special organisations. In the Netherlands, the Thrombosis Service with a network of over 70 units takes regular blood samples to test the PT level, which results in a dosage advise to the patient. Despite a strong organization, laboratory quality control, and automated, computerized dose-adjustments, for a substantial number of patients the intensity of anticoagulation is not inside the "therapeutic target range" for considerable periods of time³⁶-³⁰. Besides, standard anticoagulation therapy requires frequent venepunctures and patients' visits to the Thrombosis Service, which are time-consuming and -for some patients- inconvenient.

Recently, much effort has been undertaken to improve the methods of monitoring and management of anticoagulant therapy. Point-of-care testing of the prothrombin time (expressed as International Normalized Ratio (INR)) on capillary whole blood represents one of these developments. Point-of-care testing was initially developed for use by health care providers but after a number of user-friendly improvements it became apparent that it had the potential for patient self-monitoring and thus for patient self-management³¹,³². Effectively, patients with heart valve disease have to cope with two devices in order to regain and maintain health. We hypothesize that self-management of oral anticoagulant therapy may result in increased patient responsibility for the management of oral anticoagulant therapy and potentially improved regulation of anticoagulation. An additional advantage could be that patients can perform the test at home and are less dependent of the Thrombosis Service. A potential disadvantage could be a less optimal regulation of oral anticoagulant therapy, due to a less "professional" management of anticoagulant treatment. However, in comparable circumstances, self-management of blood glucose and dose-adjustments in insulin therapy by diabetic patients has resulted in an improved glycemic control and an (appreciated) increased


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independence from hospital or laboratory. Recent studies in other countries already show a benefit of patient self-management as compared with (general) physician-guided management. So far, no controlled comparison with a well-organized anticoagulation clinic has been conducted. Since in the Netherlands the management of anticoagulant therapy is virtually exclusively executed by specialized anticoagulation clinics (Thrombosis Service), which is thought to represent the ‘ideal’ situation, this sets the stage for a proper comparison of self-management of anticoagulant therapy with anticoagulation clinic-guided management.

1.4 HOW TO MAKE MECHANICAL HEART VALVES SAFER

This thesis illustrates the application of the concept of systems safety management on the use of devices for treatment of heart valve disease. The perspective is that of doctor and patient. Treatment failure due to device failure can be death or disability. This may be due to intrinsic or structural failure of the valve. In case of patient self-management by means of the CoaguChek®, failure of the device may be the cause. However, the intrinsic valve failure is due to shortcomings at the part of the manufacturer. CoaguChek® failure will be mostly due to human error or patient failure. The chapters two, three and four covering valve failure, and the chapters six to nine referring to the patient self-management failure, present two different sets of failure scenario’s and risk control solutions. Chapter five is of interest as it describes a substantial risk to treatment failure by means of excessive bloodloss in the postoperative phase. Due to the likelihood of occurrence and the perceived relevance of this safety threat a large body of data and information with respect to risk figures and treatment options are available. The aggregation and analysis of this information by means of a meta-analysis contributes to better decision making. So, this modus of evidence-based medicine enables safer practices, but in a distinctly different way when compared with device failure.

Another marked difference between the topics treated in the various chapters, is reflected by failure analysis methods used. Fractured valves are supposed to be a rare event, with enormous litigation consequences. Very intensive technical analysis of a single valve and/or “accident” must provide the evidence. Also the fact that post marketing surveillance and reporting of these rare events don’t seem very popular amongst the various interested parties, contributes to incomplete information. The chapter on the product life cycle and barriers describes the interdependence and intertwinemen of interests and risk management actions. Learning form a single or a limited number of accidents implies the willingness to improve design on the basis of the information derived from the failure analysis. In chapters three and four we describe that appropriate risk control actions apparently also require a relevant stimulus form the threat of litigation. In contrast with chapters two, three and four, in which the thoroughness of the technical and case analysis has to compensate for the lack of
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quantitative certainty, chapters five and eight illustrate the possibilities of clinical research. The investigator controls the number of cases in order to reduce uncertainty. It is assumed that in daily clinical practice all components described in the chapters are to be controlled by the surgeon. This implicates that handling a safety management challenge implicates the use of methods and tools from various disciplines. This approach provides a more realistic view on the difficulties and potentials of real world risk control practices, which are too frequently monopolized by a single discipline.

Secondary, each chapter gives an insight to the parties involved on how the others are dealing with the risks specifically induced by their discipline. Chapters two and six present methods frequently used by device industries, but now made accessible to clinicians and administrators. At the other hand device industries often skip relatively simple methods such as the meta-analysis or the cross-over design (chapters five and eight). Therefore, the thesis can be seen as the safety case study of the event failed heart valve treatment. Can we conclude that this safety case study improves safety for individual patients? First of all the thesis and the separate chapters intend to learn the interested reader about the occurrence of risks, the way risk information is acquired and analyzed, and how this knowledge may contribute to reduction of risks or their hazardous effects. The new safety knowledge amongst other facilities such as the availability of risk control tools and an adequate organization, and the existence of a positive safety culture may result in safer devices and practices.

1.5 REFERENCES

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