Mechanical heart valve prosthesis. Oral anticoagulation and risk factors for thromboembolism and major bleeding.

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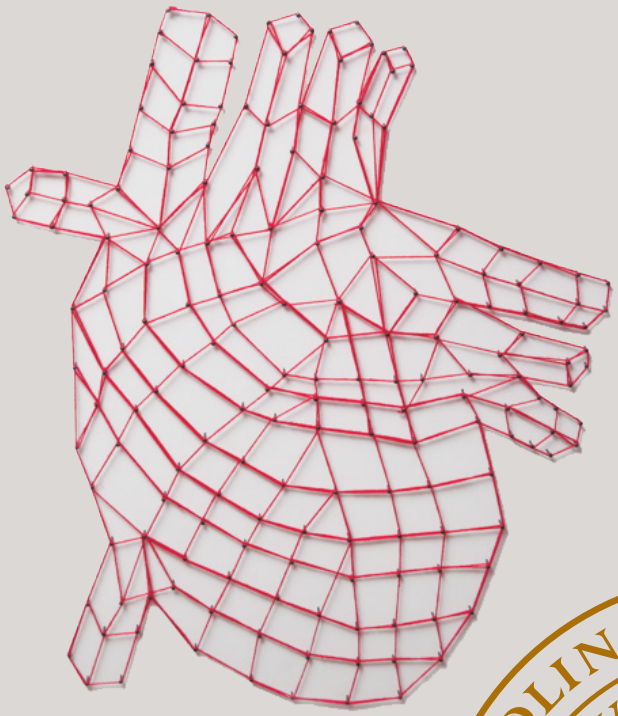

Mechanical heart valve prosthesis

Mechanical heart valve prosthesis -

Oral anticoagulation and risk factors for thromboembolism and major bleeding

Ashkan Labaf

LUND
UNIVERSITY

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Title and subtitle: Mechanical heart valve prosthesis – oral antcoagulation and risk factors for thromboembolism and major bleeding.

Abstract

Mechanical heart valves (MHV) are more durable than bioprosthetic valves; however their use requires lifelong anticoagulation treatment due to the thrombogenicity of the valve. The reported incidence of thromboembolism (TE) and major bleeding are heterogenous due to varying inclusion of patients, valve type, anticoagulation quality and INR target ranges. Morover, the association between patient-related risk factors and adverse events, and anticoagulation quality in terms of time in therapeutic range (TTR) and INR variabilty is unknown.

In paper I, we aimed to make a descriptive study anlayzing the the incidence of TE and major bleeding, and analzying risk factors for these adverse events in all patients with MHV within two Swedish centers during 2008-2012. The incidence of TE was 1.8 and 2.2 per 100 patient-years for aortic valve replacement (AVR) group and mitral valve replacement (MVR) group respecively. The corresponding major bleeding incidence was 4.4 and 4.6 per 100 patient-years respectively. Independent risk factor of TE was vascular disease and for major bleeding, previous major bleeding emerged as an independent risk factor. The standardized mortality ratio resulted in an equal risk of death compared to the background population despite the high adverse events.

In paper II, we aimed to investigate the effect of estimated glomerular filtration (eGFR) on the adverse events and mortality in the this population. The incidence of major bleeding and death increased with decreasing eGFR but not for TE. After multivariate adjustment, every unit decrease in eGFR increased the risk of major bleeding by 2%, death by 3% and the combined endpoint by 1%. The proportion of dearranged INR values, INR >3.0 and INR >4.0, and decreasing TTR were found for each decreasing eGFR stratum.

In paper 3, we analyzed surrogate markers of anticoagulation quality in terms of INR variability that measures stability and variance, and TTR that measures intensity of anticoagulation. The results showed that INR variability performs equal as TTR 2.0-4.0 for the combined endpoint, and even better for mortality. Furthermore, the risk of the combined endpoint within different levels of TTR were influenced significantly by high INR variability. Anlaysis with INR at the time of event demonstrates that the incidence rate of TE and major bleeding is lowest when INR is 2.5-3.0.

In paper IV, we conducted a nationwide study with 4,810 treatment periods with MHV to validate the results of paper I. The rate of TE for AVR and MVR was 1.3 and 1.6 per 100 patient-years respectively, and for first major bleeding event 2.6 and 3.9 per 100 patient-years respectively. Independent risk factors for TE was age and previous stroke. Atrial fibrillation and heart failure showed no correlation with TE. Similar rates of TE and major bleedings were found for AVR between INR target range of 2.0-3.0 and 2.5-3.5 (and 2.0-4.0).

This thesis demonstrates the risk of TE and major bleeding events with associated risk factors as anticoagulation quality, renal function and patient-related risk factors linked to these adverse events, and has potential implications for the care of patients with MHV.

Key words: Mechanical heart valve prosthesis, anticoagulation, International Normalized Ratio variability, time in therapeutic range, estimated glomerular filtration rate, thromboembolism, major bleeding

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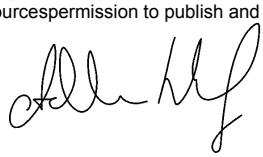
Signature  Date 2016-08-08

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Yesterday I was clever, so I wanted to change the world. Today I am wise, so I am changing myself.

- Rumi; Persian poet and Sufi mystic (1207-1273)

To Mojgan and Nelia

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List of abbrevations

AVWS	acquired von Willebrand syndrome
ADP	adenosine diphosphate
AMI	acute myocardial infarction
APC	activated protein C
ATP	adenosine triphosphate
AF	atrial fibrillation
AVR	aortic valve replacement
Bioprosthesis	biological prosthesis
cAMP	cyclic adenosine monophosphate
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
DOAC	direct oral anticoagulants
eGFR	estimated glomerular filtration rate
HR	hazard ratio
ICD	International Classification of Diseases and Related Health problems
INR	international normalized ratio
ISTH	International Society on Thrombosis and Haemostasis
LM rev	Lund-Malmö revised equation
LMWH	low molecular weigh heparin
MDRD	Modification of Diet in Renal Disease
MVR	mitral valve replacement
MHV	mechanical heart valves
NPR	National Patient Registry
PAI	plasminogen activator inhibitor
PSM	propensity score matching
PT	prothrombin time
PGI_2	prostacyclin
SBU	Swedish Council on Health Technology Assessment
SD	standard deviation
TAFI	thrombin-activated fibrinolysis inhibitor
TE	thromboembolism
TF	tissue factor
TFPI	tissue factor pathway inhibitor
tPA	tissue-type plasminogen activator
TTR	time in therapeutic range
VKA	vitamin K-antagonist
VWF	von Willebrand factor
uPA	urokinase-type plasminogen activator

List of publications

The present thesis is based in the following papers, referred to by their Roman numerals and reprinted with consent from the respective publishers.

I. Labaf A, Grzymala-Lubanski B, Stagmo M, Lovdahl S, Wieloch M, Sjalander A, Svensson PJ. **Thromboembolism, major bleeding and mortality in patients with mechanical heart valves- a population-based cohort study.** Thromb Res. 2014;134(2):354-9.

II. Labaf A, Grzymala-Lubanski B, Sjalander A, Svensson PJ, Stagmo M. **Glomerular filtration rate and association to stroke, major bleeding, and death in patients with mechanical heart valve prosthesis.** Am Heart J. 2015;170(3):559-65.

III. Labaf A, Sjalander A, Stagmo M, Svensson PJ. **INR variability and outcomes in patients with mechanical heart valve prosthesis.** Thromb Res. 2015;136(6):1211-5.

IV. Labaf A, Svensson PJ, Renlund H, Jeppsson A, Själander A. **Incidence and risk factors for thromboembolism and major bleeding in patients with mechanical heart valve prosthesis; a nationwide population-based study.** Am Heart J. In press.

Papers not included in this thesis:

Grzymala-Lubanski B, Labaf A, Englund E, Svensson PJ, Sjalander A. **Mechanical heart valve prosthesis and warfarin - treatment quality and prognosis.** Thromb Res. 2014;133(5):795-8.

Labaf A, Carlwe M, Svensson PJ. **Efficacy and safety of novel oral anticoagulants in clinical practice: a report from three centers in Sweden.** Thromb J. 2014;12(1):29.

Introduction

Anatomy and function of heart valves

The heart is an effective muscular organ that pumps blood to all the tissues of the body through a network of blood vessels. The heart is divided into four chambers, two atria and two ventricles, figure 1.

The right atrium functions as a receiving chamber where deoxygenated blood from the great veins enters. The blood then flows through the tricuspid valve into the right ventricle where the blood pumps through the pulmonary trunk to the lung vessels where the blood gets oxygenated. The blood returns through the pulmonary veins to the left atrium where it flows through the mitral valve into the left ventricle. The left ventricle, which has a thicker myocardium, receives the oxygen-rich blood and then pumps it through the aortic valve to all the tissues of the body to deliver oxygen.

The heart has two types of valves that keep the blood flowing in the correct direction. The valves between the atria and ventricles are the atrioventricular valves whereas those between the ventricles and the base of the large vessels leaving the heart are the semilunar valves. The atrioventricular valves are the mitral and tricuspid valves and prevent blood from going backwards to the atria during systole. During diastole, these valves open as a result of increased pressure from the atria as it fills with blood (preload). In order not to prolapse into the atria during systole and to hold the valve, the valves are anchored to the walls by chorda tendineae, which are attached to papillary muscles. The closure of these valves causes the first heart sound (S1). The mitral valve has two cusps and is named after the resemblance to a bishop's miter (headdress). The semilunar valves are the aortic and pulmonary valve. During systole, increased pressure in the ventricles causes the aortic and pulmonary valves to open when it is greater than the pressure in the aorta and pulmonary artery. The valves prevent in the same way backflow into the ventricles during diastole. The semilunar valves are not supported by chordae, and resemble the valves in the veins more than the atrioventricular valves. The closure of the semilunar valves causes the second heart sound (S2).

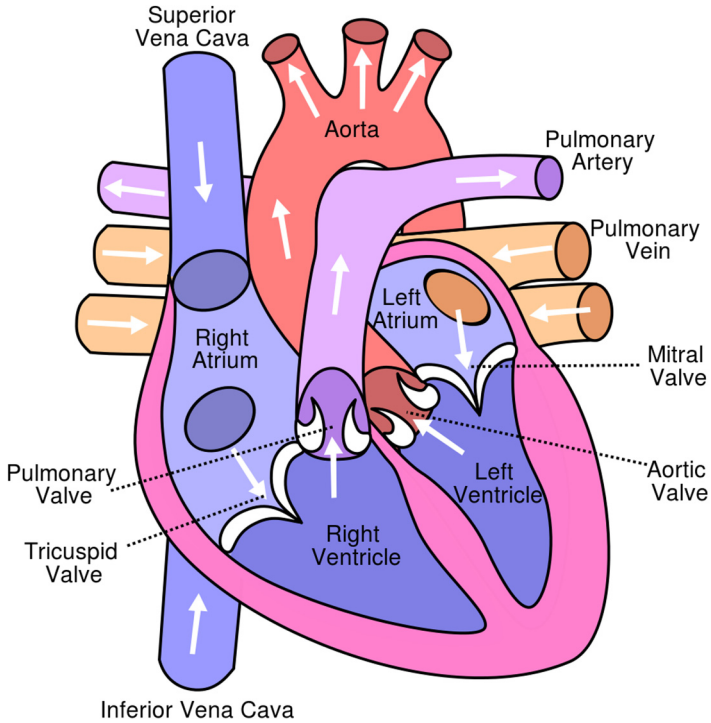


Figure 1.
Anatomy of the heart.

Valvular heart disease

Valvular heart disease affects more than 100 million people worldwide and is increasing with our ageing population. The primary causes of valve disease are degenerative (age-associated calcific valve changes) and rheumatic valve disease. The rheumatic valve disease has declined considerably in Europe and North America but it remains an issue in the developing countries. Rheumatic fever is the leading cause of acquired heart disease in children and young adults worldwide. Caused by an infection with group A betahemolytic streptococcus (GAS), which is followed by a latent period of some weeks where the illness is characterized by acute inflammation of the heart, joints, skin and central nervous system. The inflammation is primarily damaging the collagen fibrils and connective tissue ground substance. Carditis is the most feared complication, which may lead to chronic rheumatic heart disease with an increasing risk of atrial fibrillation (AF), stroke, heart failure and infective endocarditis. Referring to the damaging effect of the heart and the mild arthritis,

French physician Ernst-Charles Laségue quoted as saying *"Pathologists have long known that rheumatic fever licks at the joints, but bites at the heart."* The most common valvular lesion is mitral regurgitation while stenotic lesions are unusual in the early stages.

Approximately two thirds of all heart valve surgeries are aortic valve replacement (AVR), most often for aortic stenosis. Valvular aortic stenosis has three principal causes: congenital bicuspid valve with calcification, calcification of a normal trileaflet valve, and rheumatic disease. As long as patients remains asymptomatic when having moderate to severe aortic stenosis, prognosis is good (1). Due to the progressive nature of the disease, close follow-up is warranted though. There is strong evidence that the most important predictor of progression to symptoms is the Doppler aortic jet velocity. Patient survival is 84% at 2 years when jet velocity is less than 3 m/sec, compared with only 21% when jet velocity is greater than 4 m/sec (2), figure 2.

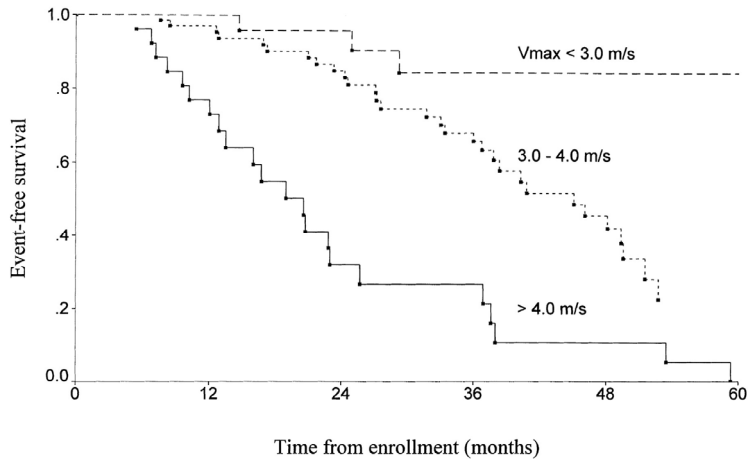


Figure 2.
Cox regression analysis showing event-free survival in groups defined by aortic jet velocity at entry (p <0.0001 by log-rank test).
Catherine M. Otto et al. Circulation. 1997;95:2262-2270

Mitral regurgitation can be caused by mitral valve prolapse, rheumatic heart disease, infective endocarditis, annular calcification, cardiomyopathy and ischemic heart disease. These causes influence the mitral valve apparatus in different ways and also determine the strategies for surgical correction. Surgical repair of the valve is always recommended whenever it is possible, instead of mitral valve replacement (MVR). The risk of mortality and morbidity is inferior with MVR compared to MVR, due to operation risk, the risk of thromboembolism (TE) and anticoagulation, and the risk of left ventricular deterioration after MVR. Mitral stenosis is less common in the western world, and the predominant cause is rheumatic fever.

Mechanical heart valve prosthesis

History of mechanical heart valves

In 1989, one of the pioneers of cardiac surgery declared that the properties of an ideal valve replacement are durability, no thrombogenicity (anticoagulants not required), no inherent gradient and easy to implant. These commandments are unfortunately not all satisfied today according to the ideal profile described by the late Dr Dwight Harken.

With the development of the heart-lung machine in the 1950's it suddenly became possible to implant valve replacements. Implants took off in a rapid pace, which was described as "the great valve rush of the late 1950s and early 1960s" by Dr L. Henry Edmunds (3). By the end of the 1960's the essential categories of prosthetic heart valves were introduced and all the major complications of valve replacement had occurred (4). When Dr Jack Bokros, a materials engineer, fabricated a hollow ball of pyrolytic carbon for the DeBakey-Surgitool valve in 1969, which was originally developed for the encapsulation of nuclear fuel rods, it was a landmark in mechanical valve development. This would become the principal material used for the mechanical heart valve prosthesis for many years to come (5).

Caged ball valves

In 1952, Dr Charles Hufnagel of Georgetown University Medical Center implanted the first artificial heart valve. Hufnagel's invention was a plastic tube with a plastic ball in the center- or "caged ball", which was implanted in the descending thoracic aorta in a patient with aortic insufficiency in a 30-year-old woman (6). A non-suture technique was used in a quick manner as no heart-lung machine was used. This technique was obviously unsuccessful and did not provide any benefit to a patient with aortic insufficiency. Approximately 7 years after Dr John Gibbon performed the first successful closure of an intracardiac defect with a heart-lung machine in 1953, Dr Dwight Harken implanted a caged ball valve in the subcoronary position in a patient with aortic stenosis. Almost simultaneously in 1960, Dr Albert Starr implanted a bulky valve with a cage of methacrylate and a silicone elastomer rubber ball, in a 52-year-old man with calcific mitral stenosis. This patient actually survived

for 10 years with the prosthetic valve, dying unfortunately in a fall from a ladder while painting his house. These total valve replacements were the real breakthroughs that were to change the specialty of cardiac surgery over the next 60 years (7).

Dr Albert Starr and Mr Lowell Edwards, a retired pump engineer developed a series of ball valves from the Edwards laboratories for the next decade. The silicone ball moved freely within the confines of a three-strut alloy cage, which in theory would prevent thrombus formation on the sewing ring from extending onto the occluder (8). Although the tilting disc valves and bileaflet valves that were developed in the 1970's offered better hemodynamic conditions and fewer adverse events such as thromboembolism (TE), some extremely durable Starr-Edwards prosthesis provided quite satisfactory hemodynamic function and continues to be used, especially in poor countries due to the low cost.

Tilting disc valves

The main purpose of the tilting disc valve was to restore the central blood flow that was absent in the cage valves. In the late 1960's, Dr Viking Björk, heart surgeon at Karolinska Institute and Donald Shiley introduced the flat disc valve, which was the first successful example of the tilting disc design. This was extremely successful worldwide with almost 300,000 aortic and mitral prosthesis valves implanted between 1969-1986 (9). In order to make a larger flow-through orifice (minor orifice) and to reduce the risk of thrombus formation, it was further updated to convexo-concave design. However, within a few years these implantations were associated with fractures at the weld site of the small C-shaped outflow strut, which resulted in escape of the disc, resulting in embolization, massive regurgitation and often death (10). By 2004, outlet strut fractures had been reported in 633 Björk-Shiley convexo-concave valves (0.7% of 86 000 valves) (11). It was initially thought that the strut rupture was the result of faulty welding in the outflow strut, but careful engineering analysis indicated that the large diameter in these prosthetic valves there can be "leverage loading" on the center of the small outflow strut during leaflet closure (12).

The Hall-Kaster valve that was developed by Dr Karl Victor Hall of Rikshospitalet Oslo and Robert Kaster, had a disc made of carbon pyrolytic coating with a small central perforation for a thin metal strut that guides the disc during opening and closing (13). After a minimal change of engineering of the valve, the manufacturing was assumed by Medtronic and has been one of the most commonly implanted tilting disc valves with no reports of structural failure.

Bileaflet Valves

The main purpose of the bileaflet design was to avoid the high profile that was associated with the bulky caged ball valves that were available in the 1960's. These prosthetic valves provide a more symmetric, central and non-turbulent blood flow. There were was also made of pyrolytic carbon coated with graphite and consists of two leaflets hinged on a ring. Although some bileaflet valves had been designed and even implanted into a limited number of patients in the 1960's (14), it was the St Jude Medical valve introduced in 1977 which outnumbered all other prosthetic valves. It is the single most commonly implanted mechanical valve to date (15) and although there have been changes in the sewing ring over the years, it is remarkable that the design is virtually unchanged from its original model. In 1986, the Carbomedics valve was introduced which was very similar to the St. Jude valve, but the housing could be rotated within the sewing ring.

In order to reduce the complications that were associated with existing mechanical valves such as inadequate hemodynamics in small aortic sizes, unexplained hemolytic anemia, pannus overgrowth and most commonly thromboembolic episodes, new generation mechanical valves were introduced.

The On-X prosthetic valve that was introduced in 1996, used a pure pyrolytic carbon construction and smoothly contoured surfaces. The inlet flare, fully opening leaflets, and the maximized use of the annulus improved hemodynamic flow. While the annulus support and leaflet guarding reduced the risk of pannus overgrowth, the reduced turbulence, pure pyrolytic carbon and smooth backflow patterns acted to reduce hemolysis. The main purpose of the design was to reduce the thromboembolic complications, which rightly have yielded in better mid- and long-term clinical results (16, 17).

Figure 3. Mechanical heart valves.
1: Starr-Edwards 1964, 2: Björk-Shiley 1971, 3: St:JudeMedical Masters 1994, 4: MCRI On-X 1996.

Valve-related complications in mechanical valve prosthesis

Through the history of prosthetic heart valves there have been different conserns in different time periods. In the late 1960's, 1970's and early 1980's, manufacturers started to develop mechanical and chemically preserved xenografts, and tissue valves. Their common design was founded on an annular sewing ring to support the insertion into the native annulus. The sewing ring and the following opening impedance produced pressure differences between 5-25 mmHg depending on the flow across the valve, valve size, anatomic location and obviously design. This disadvantage was accepted because the prosthetic valves improved hemodynamic conditions and symptoms in comparison to the native valves. As the perioperative mortality and morbidity steadily decreased, cardiologists and heart surgeons realized that despite the improved mortality and morbidity following the newer prosthetic valves, there were still a cumulative and persistent rate of complications and mortality.

During a long time of period numerous manufacturers produced new prosthetic heart valves that were supposed to be superior in terms of early- and midterm mortality and morbidity, but all of the valves lacked data on long-term complications. Many prosthetic valves were inserted into patients without complete preliminary testing which resulted in many early failures, whereas other required longer follow-up time to expose the increased incidence of TE or valve dysfunction. The follow-up data and reports of comparisons between the different valves were not facilitated by the heterogeneous collection of patients with different definitions of complications. This gave rise to a committee-generated document that attempted to define valve-related complications and to offer guidelines for collection of follow-up information (18). Comparisons were however aggravated due to the differences in patient demographics and standards of post discharge care such as anticoagulation quality in the reports.

To briefly summarize the difference in the selection between MHV and biological prosthesis (bioprosthesis), MHV are more durable than bioprosthesis due to calcific or non-calcific tissue deterioration of the bioprosthesis. Because of the thrombogenecity of the MHV, vitamin K antagonists (VKA) are necessitated which concomitantly increases the risk of bleeding. The risk of thromboembolism (TE) is however low in bioprosthetic valves and do not require treatment with VKA.

Although guidelines are shifting away from arbitrary age limits when selecting between a MHV and a bioprosthesis, it remains the most significant factor. Other determinant factors are the risk of anticoagulation-related complications as bleeding and TE, risk of structural valve deterioration, the risk of an eventual redo valve surgery, patient factors and preferences. In patients between 60-70 years old, either prosthesis is acceptable according to guidelines with one randomized trial comparing older models of MHV and biological valves that resulted in no difference in long-term survival (19) whereas two other randomized trials favored MHV (20, 21).

Recently, a propensity score matched cohort between 50-69 years comparing mechanical vs. biological prosthesis demonstrated better long-term survival of patients who received a MHV (22) with no difference in survival in patients between 60-69 years. While these and other studies support the use of MHV(23) there are publications that indicate that bioprosthesis could be considered for patients down to 50 years of age (24, 25).

Thromboembolism

TE is a major cause of morbidity and mortality in patients with MHV. The assessment of TE in patients with MHV is slightly complicated due to the heterogeneous results over the years. Due to the variability of thromboembolic episodes from one study to another, it is therefor obvious that factors other than the valve model is accountable for the risk of TE. There could be significant factors such as patient-related risk factors, anticoagulation quality and intensity, compliance, length of follow-up and heterogeneous ways of reporting complications that could influence the risk of TE. Although there are some differences between the types of valves (caged-ball, tilting disc etc) regarding the risk of TE, prosthesis cannot be conveniently categorized by design and model to determine thrombogenicity. Earlier reports with older models of the bileaflet valves(26-28) demonstrated an approximate event rate of 1-2%/patient-year, whereas more recent studies have included younger patients with less comorbidity and obviously newer generation MHVs. These studies (29-31) reported an event rate of 0.3-0.8%/patient-year with various INR targets. Also, the patients enrolled in these studies were selected through inclusion and exclusion criteria's and probably not representative of the clinical population. Furthermore, the European and American guidelines support that certain patient-related risk factors should imply revising INR target upwards to reduce the risk of TE (32-34). In the presence of previous TE, AF, mitral stenosis of any degree and left ventricular ejection fraction <35% guidelines recommend that the target INR should be increased with 0.5 in patients with AVR. There is however no evidence that complying with these guidelines will decrease the risk of TE. This recommendation is based on an outdated study with older models of MHV and high anticoagulation intensity (35) that showed an increased risk of TE in the presence of these risk factors, but is still mainly based on expert recommendations.

Pathophysiology of thrombosis

The pathogenesis of intracardiac thrombus formation in patients with MHV is complex. Rudolf Virchow proposed already in the 19th century that triad of events are needed for thrombus formation. The triad as we know it today is endothelial

dysfunction, hemodynamics and abnormal hemostasis. These variables with the addition of a fourth component, an artificial surface, have indeed a major role in the mechanism of thrombus formation. The prosthetic valve itself is not the only thrombogenic component, but also the perivalvular excision tissue, sewing ring and sutures may have an influence.

The artificial surfaces and materials used have different thrombogenic properties due to surface topography, critical surface tension, chemistry and physical structure (36). In general, artificial surfaces that have a net positive charge are essentially adsorptive of plasma proteins and blood cells. This has been demonstrated with electron microscopy that a thin film of plasma components develops very quickly as artificial surfaces were exposed to blood. Fibrinogen is among the first proteins to be adsorbed on the surface, and the surface concentration may exceed the normal concentration in blood by 100-fold (37). There is thus support that the surface-bound fibrinogen determines the relative thrombogenicity. The surface-bound fibrinogen stimulates platelet aggregation that also occurs at an early stage. The activation of platelets as with plasma proteins, depends on physical characteristics and electrical charge. In vivo, surface conditions as shear stress and surface tension affects the platelet activation (36). There is evidence that artificial surfaces, in particular negatively charged ones, activates the intrinsic pathway by the binding of factor XII which leads to activation of prekallikrein, factor XI and high-molecular-weight kininogen (38).

The endothelial factors include the biocompatibility of the prosthesis itself, and especially between the prosthesis and the suture zone. The endothelialization normally takes place the first weeks to months where the risk of thrombus formation is increased before it is completed. Although the endothelial cells have thrombo-resistant properties, the risk of TE in patients with MHV is considerably increased compared to native valves. Thus, blood flow geometry must play a central role in the mechanism of thrombus formation. There is however theories that there could be chronic endothelial-neoendothelial cell dysfunction that can influence the thrombogenicity. Early observations demonstrated that the combination of blood stasis and endovascular damage or high concentration of coagulation factors was immensely thrombogenic (39, 40).

The hemodynamics associated to the prosthesis with regards to gradient and the profiles are believed to increase the risk of TE. Older generation MHVs with higher profiles are linked to increased shearing force and prevent the natural and normal laminar flow. A prosthetic valve in the mitral position is associated with nearly a 2-fold risk of TE compared to a valve in the aortic position(41). This is particularly due to stagnant flow and hemodynamics, but could also be influenced by the high incidence of concomitant left atrial enlargement, AF and reduced left ventricle function. The hemodynamics is likely the main determinant of these variables, since a

MHV in the tricuspid position is 20 times more thrombogenic than left-sided prosthesis (42).

Valve thrombosis

Valve thrombosis is the most feared complication of valve replacement surgery in early and long-term management and can result in functional stenosis or regurgitation. This is a rare but life-threatening condition that occurs 0.03-4.3% per year (43). The prosthetic valve obstruction can be caused by thrombus formation, pannus ingrowth or both (44). It is important to distinguish between the conditions, since thrombolysis will not be effective in pannus ingrowth. Treatment of valve thrombosis includes surgery with valve replacement, fibrinolytic therapy or heparin treatment. The choice of therapy is dependent on valve location, thrombus size, reoperation risk and the risk of TE following fibrinolytic therapy (32). A review demonstrated that for left-sided obstructive valve thrombosis, fibrinolysis was efficacious in 82% of cases, but with an associated 10% mortality and a 12.5% risk of systemic TE (45). Because of the high complication rate, fibrinolysis is regarded as second line therapy, reserved for patients with contraindications to surgery.

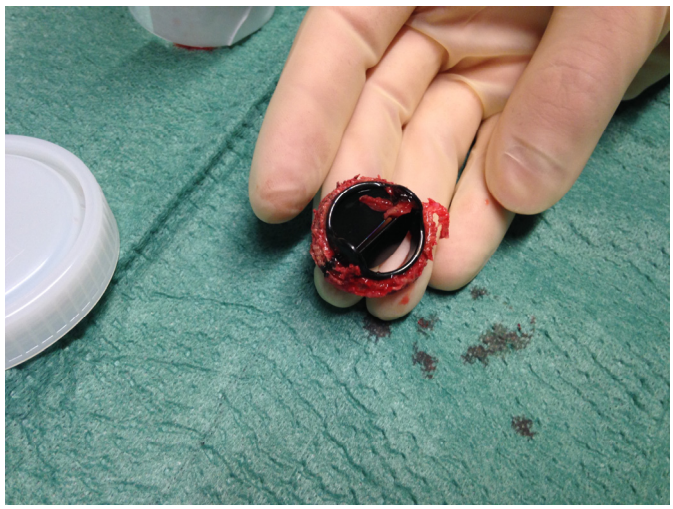


Figure 4.
Carbomedics valve prosthesis in the aortic position in a 70-year old male with abnormal valve motion and obstruction on echocardiography which proved to be pannus formation on one of the leaflets. Photograph and permission of Dr Shahab Nozohoor.

Bleeding

The disadvantage of treatment with VKA is the associated bleeding risk. The major bleeding risk in patients with MHV, is above all dependent on patient-related risk factors and the intensity and quality of anticoagulation treatment (30, 31), more than the valve itself. A systematic review of patients receiving VKA due to AF showed an incidence of 2.0 per 100 patient-years for major bleeding events (46). There have been trials comparing different target INR intervals to investigate if lowering the target values will decrease the bleeding events without a significant increase in thromboembolic events. Three studies (30, 31, 47) managed to show that lowering the INR target compared to standard INR intervals would decrease the bleeding events without increasing thromboembolic episodes.

Furthermore, in 50-95% of patients with MHV there is evidence of intravascular hemolysis. Although anemia is unusual, subclinical hemolysis is a frequent finding in normal functioning prosthetic valves (48). Turbulence of flow with high shear-stress forces and abnormal flow jets through the prosthetic valve are believed to be the causes of this kind of hemolysis (49).

Heyde's syndrome is the association between calcific aortic stenosis and gastrointestinal bleeding due to angiodysplasia, which Edward J. Heyde suggested already in 1958 (50). It has been demonstrated that the loss of the high molecular weight multimers of the von Willebrand factor (VWF), which play an important factor in the primary hemostasis may be a major contributing factor (51). Acquired von Willebrand syndrome (AVWS) is associated with increased bleeding risk and especially gastrointestinal bleeding. AVWS has been associated with aortic stenosis, mitral regurgitation and recently even in patients with prosthesis dysfunction (52). The association between paravalvular leak in patients with transcatheter aortic valve replacement (TAVR) and loss of high molecular weight multimers of the VWF were recently reported in the study of van Belle (53). It remains to be seen whether this association is a contributing cause of increased bleeding in patients with MHV with prosthesis dysfunction.

Intensity of anticoagulation

Recommendations regarding the intensity of anticoagulation treatment have changed tremendously through the years. Until the 1990's, a target INR of 3.0-4.5 was commonly used for all patients with MHV. Given that there are long-term data on the most used models, guidelines have categorized the thrombogenicity of the valves in order to choose appropriate INR target. Current guideline recommendations from Europe and North America are summarized in table 1-3. As mentioned earlier, there

has been randomized studies comparing INR ranges within same model of MHV to reduce complication rates and balancing thromboembolic and major bleeding events. The GELIA trial (29) randomized patients into three pre-specified overlapping INR ranges (3.0-4.5, 2.5-4.0, 2.0-3.5) in patients with AVR, MVR and combined AVR and MVR. INR ranges were wide, overlapping and the mean obtained INR values between the groups were close to each other. The authors found no significant differences between the groups with regards to TE and bleeding events. The ESCAT trial (30) randomized patients to lower and narrower INR range, 1.6-2.1 for AVR and 2.0-2.5 for MVR or double valves with INR self-management. The events were few (6 TE, 16 major bleedings) and resulted in no significant difference but a numerically higher major bleeding rate in the standard INR group. The LOWERING-IT trial (31) randomized low-risk AVR patients into INR range 1.5-2.5 or standard care 2.0-3.0 for a median follow-up time of 5.6 years. Only one and three thromboembolic events occurred respectively and a significant higher major bleeding risk, 6 versus 16 events, favoring the low target INR. The PROACT trial (47) investigated the same INR targets as the LOWERING-IT trial in patients with the On-X mechanical valve in aortic position with the addition of aspirin in all patients. A total of 190 patients in the lower group and 185 patients in the standard care group were randomized with an average follow-up of 3.8 years. The lower group experienced significantly lower bleeding events, with similar incidence of thromboembolism and mortality. The addition of aspirin may have contributed to a slightly increased incidence of major bleeding with no significant effect in TE-events.

These studies exhibit that with newer generation MHV in the aortic position and without an excess of comorbidity in the patients, anticoagulation intensity can be narrowed to lower levels with a significantly decreased risk of bleeding events and without an excessive incidence of TE. Some important aspects of these studies must be pointed out before extrapolating to other groups of patients. Firstly, the self-monitoring INR measurements were thoroughly performed by the patients, which have been shown to reduce variability and improve outcomes (54, 55). Secondly, patients enrolled in these studies were relatively free from other comorbidities, which can also alter the risk of events. Thirdly, two of these studies had very few events, which implies that statistical power was limited.

Table 1. European Society of Cardiology guidelines 2012.

	Patient-related risk factors [b]	
Prosthesis thrombogenicity [a]	No risk factor	Risk factor ≥1
Low	2.5	3.0
Medium	3.0	3.5
High	3.5	4.0

[a] Prosthesis thrombogenicity: Low: Carbomedics, Medtronic Hall, St Jude Medical, ON-X; Medium: other bileaflet valves; High: Lillehei-Kaster, Omniscience, Starr-Edwards, Bjork-Shiley and other tilting-disc valves. [b] Patient-related risk factors: mitral or tricuspid valve replacement; previous thromboembolism; atrial fibrillation; mitral stenosis of any degree; left ventricular ejection fraction < 35%.

Table 2. ACCP Guidelines 2012.

- In patients with MHV in aortic position guidelines recommend VKA therapy with a target range of 2.0-3.0 over lower INR targets (Grade 2C), and over higher INR targets (Grade 1B)
- In patients with MHV in mitral position guidelines recommend VKA therapy with a target range of 2.5-3.5 over lower INR targets (Grade 2C)
- In patients with MHV in both aortic and mitral position guidelines recommend VKA therapy with a target range of 2.5-3.5 over INR target of 2.0-3.0 (Grade 2C)
- In patients with MHV in the aortic or mitral position, guidelines recommend adding over not adding an antiplatelet agent such as low-dose aspirin to the VKA therapy (Grade 1B). Guidelines emphasize caution in patients with previous bleeding history
- Factors such as the presence of AF, low left ventricular ejection fraction, older age, and a history of prior thromboembolism have been suggested to increase risk of thromboembolic complications. However, no evidence exists demonstrating that higher INR targets have additional benefit over harm in these patients.

Table 3. AHA/ACC guidelines 2014.

	INR target	INR target	Recommendation /evidence
	2.5	3.0	
AVR, no risk factors	X		1B
AVR, risk factors [a]		X	1B
MVR		X	
Addition of low-dose Aspirin			1A
DOAC			3B

DOAC; direct oral anticoagulants (thrombin inhibitors and anti-Xa agents), AVR; aortic valve replacement, MVR; mitral valve replacement. [a:] atrial fibrillation, previous thromboembolism, left ventricular dysfunction, hypercoagulable conditions and older generation mechanical AVR.

Hemostasis

History of blood coagulation

The ancient Greeks already recognized the formation of thrombi when Hippocrates and Aristotle postulated that the phenomenon was caused by cooling when shed blood was observed (56). Remarkable understanding and knowledge of the mechanisms of the blood coagulation has been made during the past 60 years. In 1905, all the evidence summarized until that time was considered in "the classic theory of blood coagulation"(57), which was based on four substances that were involved in the coagulation system, namely thrombokinase, prothrombin, fibrinogen and calcium.

As technology evolved, single patient cases with deficiencies in the coagulation system with simple laboratory tests could be observed and reported. When protein chemistry was introduced in the 1970s, scientist were able to isolate and characterize coagulation factors and inhibitors from plasma that obviously made a great difference. The lack of the coagulation factors were observed and discovered in patients with inherited deficiencies before laboratory testing was possible. Although hemophilia was described already in 1850 as a clinical entity with obvious X-linked inheritance, it was in 1936 that Patek and Stetson reported that there was a lack of substance in hemophilic blood that prolonged the bleeding time (58). When normal plasma was added to the hemophilic blood, the clotting time was shortened and the agent later was named antihaemophillic factor (AHF) or factor VIII. Numerous clotting factors were discovered in patients with various deficiencies during 1940-50s with the names deriving from the investigators or the patients. Same clotting factors were being named by different investigators which led to a consensus report of an international committee (The International Committee on the Nomenclature of Blood Coagulation Factors) in 1954 (59). A system of Roman numerals was adopted for each coagulation factor rather than eponyms.

Quick's one-stage prothrombin time (PT) was already published in 1935 and was developed to measure prothrombin (60). He later discovered that added fresh plasma from patients from coumarin treatment (VKA) influenced the test that was instrumental for the discovery of coagulation factors V, VII and X. As new coagulation factors were being discovered, there was a need for revision of the classic

theory to fit the new information. There were numerous investigations to study the sequences of coagulation and several schemes were proposed. When the waterfall or cascade hypothesis was proposed in 1964 (61, 62), it was a major advancement and a much simpler understanding of the mechanism of the coagulation system. The concept of blood coagulation as a cascade of eight enzymatic reactions leading to the formation of fibrin, with involvement of activation of coagulation factors with positive and negative feedback was ultimately the theory that constituted the basis for the coagulation cascade as we know it today. Modifications to the cascade theory were made continuously as the clotting factors were being better defined. Meanwhile in 1965, a familial thrombotic tendency was found that eventually led to the finding of antithrombin and the association of antithrombin deficiency (63). Similarly, the deficiency of the anticoagulant effect in plasma such as protein C, protein S and a mutation in the factor V gene (factor V Leiden) led to discovery of each factor (64-66).

The action of VKA was already established in the 1920s by the Danish scientist Henrik Dam when the absence of vitamin K resulted in hemorrhage in chickens. The diseased chicks were found to have deficient levels of prothrombin and later on the other vitamin K-dependent factors (factors VII, IX and X). In the late 1930s, in the search of a new rat poison, dicoumarol was synthetized and the patent was assigned to the Wisconsin Alumni Research foundation. The most potent dicoumarol was labeled "warfarin", a name that was derived from the organization's initials. Currently, about 2% of the population in Sweden are treated with warfarin (67).

Hemostasis

The ability of the blood to transform components to solid form represents a network of enzymatic activation and inhibition. The physiological process that stops bleeding from the bleeding blood vessel while normal flow is preserved elsewhere in the blood stream is called hemostasis. A need of rapid and efficient response is clearly required for survival in a bleeding person. A delicate system must be provided in order to prevent extensive thrombus formation and the need of removal of clot formation when vessel injury is repaired. This system needs to be balanced rigorously between the components of the blood and blood vessel. There are five major components involved in the hemostatic system; platelets, coagulation factors, coagulation inhibitors, fibrinolysis and blood vessels. Traditionally, the hemostasis is divided into primary and secondary hemostasis. In site of injury, platelet aggregation and platelet plug formation is part of the primary hemostasis. Secondary hemostasis refers to the fibrin formation, which is generated by the proteolytic coagulation cascade. These two processes occur simultaneously and interact with each other. The fibrinolytic

system dissolves clot formation during the process of healing and plays a significant role in the hemostatic system.

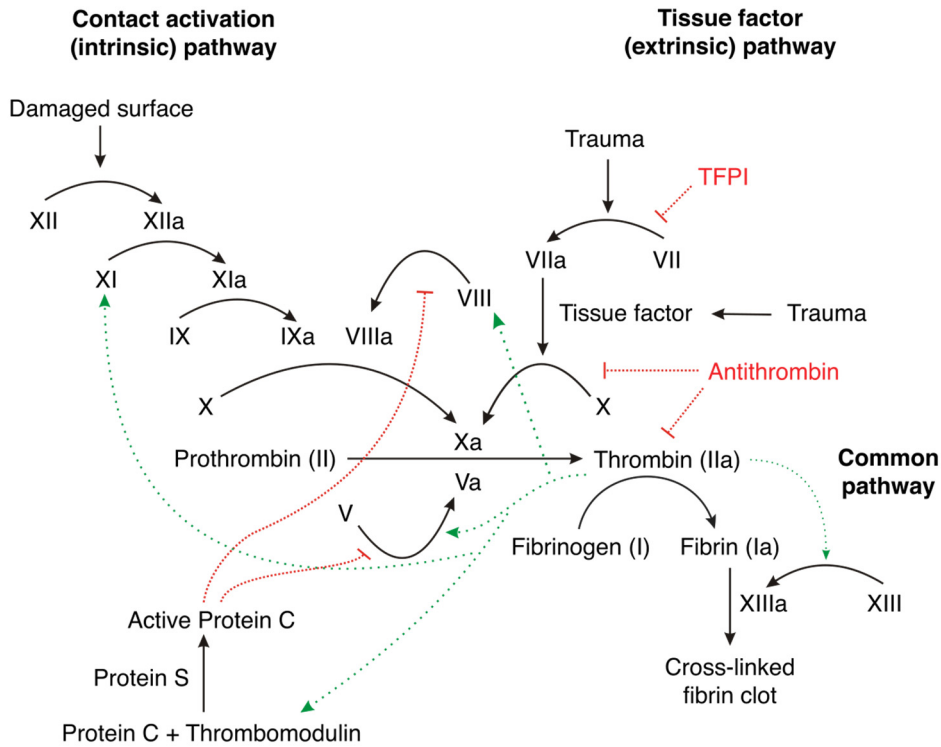


Figure 5.
The coagulation cascade.

Platelet function

Platelets are small, discoid anuclear cell fragments with glycoproteins on the surface coat that are important in the reactions of adhesion and aggregation. The key for all these receptors is that the abilities of adhesion (platelet-vessel wall), aggregation (platelet-platelet) and release reactions only take place in the event of vascular injury. Endothelial cells provide a barrier for platelets in the blood stream with various types of collagen present in the subendothelial matrix. Plasma VWF is synthesized mainly in the endothelial cells and is involved in platelet adhesion and aggregation. The binding of glycoprotein Ib-IX-V complex to VWF leads to adhesion to the subendothelium and also exposes the binding site for IIb/IIIa which is a receptor for fibrinogen leading to the platelet aggregation (68). Platelets contain different types of

storage granules that have important roles in the aggregate formations and the positive feedback system for promoting platelet activation. These granules contain clotting factors, VWF, platelet-derived growth factor, adenosine diphosphate (ADP), adenosine triphosphate (ATP), Thromboxane A_2, serotonin and calcium. ADP and Thromboxane A_2 release play important roles in the positive feedback loops for the amplification of platelet activation and aggregation. The release of thromboxane A_2 is inhibited by substances that increase the level of cyclic adenosine monophosphate (cAMP), such as prostacyclin (PGI_2) that is synthetized by the endothelial cells. Thus the platelet activation is balanced and mediated by cAMP and its effect on these major mediators. Released ADP binds to receptors $P2Y_1$ and $P2Y_{12}$ to mediate further aggregation and propagation of the platelet plug. Following platelet activation, there are links to activation of the coagulation cascade by the exposed membrane phospholipid (platelet factor 3). These calcium-dependent reactions involve factors IXa, VIIIa and X in the formation of factor Xa, and secondly the formation of thrombin from the interaction of factors Xa, Va and prothrombin (II).

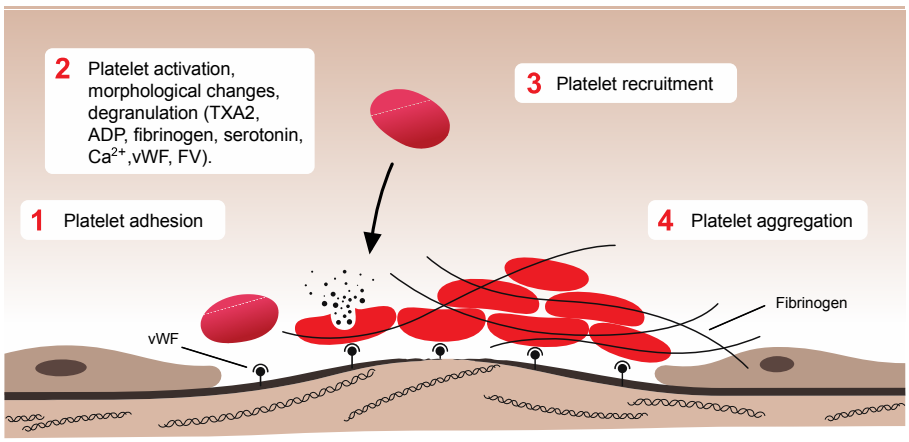


Figure 6.
Primary hemostasis. TXA2 = thromboxane A2, ADP = adenosine diphosphate, vWF = von Willebrand factor. With permission from Casper Asmussen.

Initiation and amplification

Blood coagulation is a system of enzymatic reactions in which relatively few initiation substances sequentially activate by proteolysis a cascade of precursor proteins, which finally leads to the formation of fibrin to prevent hemorrhage. The coagulation cascade is a complex network of circulating inactivated coagulation factors, and the interaction with anticoagulants in which amplification and negative feedback play central roles to ensure a localized and limited production (69), figure 5. The scale of

amplification is tremendous (e.g. 1 mol of activated factor XI through sequential activation of factors IX, X and prothrombin may generate up to 2 x 10^8 mol of fibrin). All coagulation factors except factor XIII, are serine proteases which means that their ability of hydrolyze peptide bonds are dependent on the amino acid serine at the active center.

The initiation phase, classically referred to as the extrinsic pathway starts following vascular injury, when blood is exposed to extravascular tissues, which are rich in tissue factor (TF). TF is expressed on fibroblasts of the adventitia, in the small muscles of the vessels and on micro particles in the blood stream. TF forms a complex with cofactor VIIa and activates factor X and IX. The activation of factor Xa with the presence of cofactor Va form a thrombokinase complex on TF-expressing cells, which activates prothrombin to thrombin (70). Thrombin, which is the central serine protease in the coagulation cascade, has several central roles in the hemostasis. Thrombin hydrolyses fibrinogen that releases fibrinopeptides A and B to form fibrin monomers. These monomers link together to form loose insoluble fibrin polymer. Factor XIII, which is activated by thrombin and calcium, stabilizes the fibrin polymers. Thrombin also activates factor XI and V, and cleaves factor VIII from its carrier VWF which increases the formation of VIIIa-IXa and hence of Xa-Va (71, 72). Thus, an amplification phase is generated by the effect of thrombin on the cofactors and platelet activation that have adhered to the site of injury.

Earlier theories suggested that the intrinsic factor XI-XII pathway only served as an amplification loop to enhance the extrinsic TF pathway. Recently, it has been showed that these pathways occur simultaneously in mice. The traditional theory of the intrinsic pathway included autoactivated factor XII cleaving prekallirein into kallirein, which in turn lead to the activation pathway of factor XI, IX, X and finally thrombin. New insights have discovered that other major triggers of the intrinsic pathway are involved, namely, collagen (73), linear phosphate polymers termed polyphosphates (74), and neutrophil extracellular traps (75). Cell and platelet derived polyphosphates are suggested to bind to factor XII and which seems to increase the fibrin clot stability (76). Subsequently, this could explain why high levels of factor XII is associated to thrombosis and why deficiency in factor XII leads to unstable clots and embolization. Furthermore, it appears that these polyphosphates also act as cofactor for thrombin-mediated activation of factor V and XI, and inhibits clot fibrinolysis.

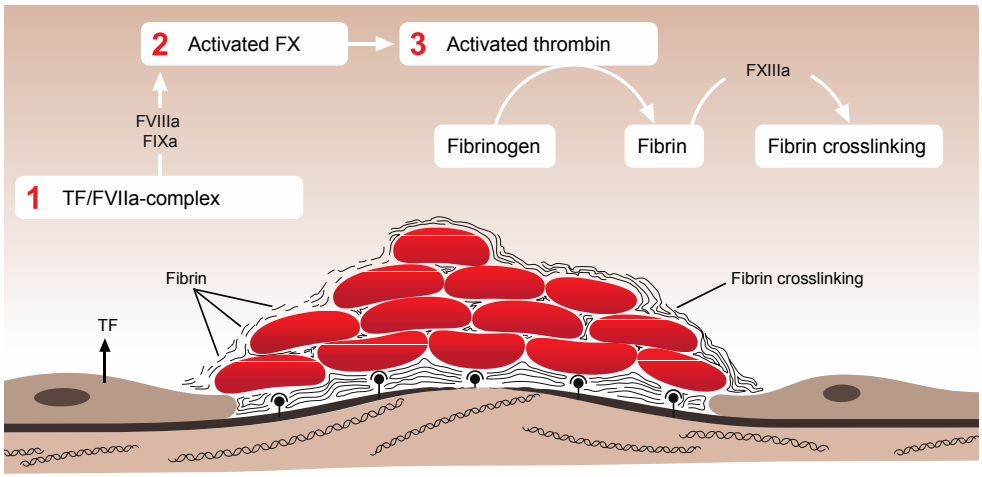


Figure 7.
Plasma coagulation. TF = tissue factor. With permission of Casper Asmussen.

Natural anticoagulants

The down-regulation and control of the hemostasis is a complex network of anticoagulants in the blood that interacts with the components of the coagulation system. Studies in patients with deficiencies and genetically modified mice have shown the importance of suppressors of the coagulation mechanism to prevent uncontrolled clot formation. An important inhibitor is tissue factor pathway inhibitor (TFPI) which is synthetized in the endothelial cells, and accumulates in the site of injury (77). The inhibition of factor Xa, VIIa and TF limits the pathway of clot formation by forming the quaternary complex. Circulating serine proteases such as antithrombin (most potent), heparin cofactor II and CI inhibitor eliminate activated coagulation factors by binding to their active sites (78). These serine proteases exert inhibitory effect mainly on thrombin.

Protein C and protein S are inhibitors of factors V and VIII. Thrombin binds to an endothelial cell surface receptor, thrombomodulin on intact endothelial cells and then activates protein C. Activated protein C (APC) establishes proteolytic inactivation of factor Va and VIIIa, thus preventing further thrombin generation (79). Protein S enhances the action of protein C by binding to protein C on the platelet surface. These inhibitors are vitamin K-dependent serine proteases and hence inhibited with treatment of vitamin K-antagonists such as warfarin. Patients with factor V Leiden has a mutation that leads to the formation of factor V which cannot be cleaved by APC and subsequently not support the APC-driven inactivation of factor VIIIa. Individuals heterozygous or homozygous for this mutation have a 5 and 50-fold

increased risk of venous thrombosis, respectively. This mutation is usually called APC-resistance, which however embraces a wider definition.

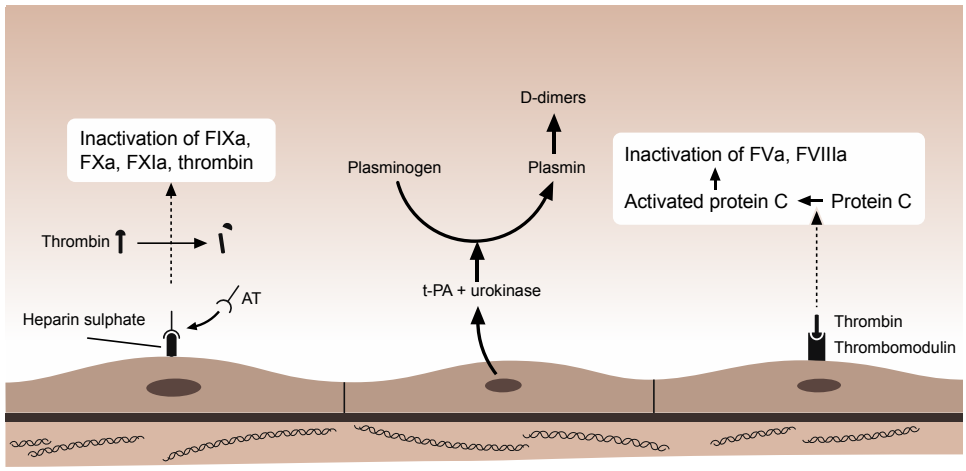


Figure 8.
Natural anticoagulants and fibrinolysis. AT = anti-thrombin, t-PA = tissue plasminogen activator. With permission from Casper Asmussen.

Fibrinolysis

Fibrinolysis is the process where thrombi are dissolved during healing or to prevent clots in healthy blood vessels. This is like the coagulation process a normal hemostatic response to vascular injury. A proenzyme, plasminogen is converted to the serine protease plasmin by activation from extrinsic (tissues) or intrinsic (vessel wall). Release of tissue-type plasminogen (tPA) and urokinase-type plasminogen activator (uPA) binds to fibrin from endothelial cells and are the most important routes (80). This will enhance the conversion of thrombus-bound plasminogen into plasmin. Furthermore, activated protein C promotes fibrinolysis by inactivating plasma inhibitors of tPA. Meanwhile, thrombin inhibits fibrinolysis by activating thrombin-activated fibrinolysis inhibitor (TAFI) that prevents plasminogen from binding to fibrin. tPA is inactivated by plasminogen activator inhibitor (PAI). Plasmin has the ability to digest and cleave peptide bonds in fibrin and fibrinogen, factor V and VIII and many other proteins. The cleavage of fibrin produces a variety of degradation products, including cross –linked fibrin –D- that can be measured in plasma. This is used as an unspecific marker for venous TE in the clinical practice.

Prothrombin time

The prothrombin time (PT) main uses are to monitor treatment with coumarins (VKA), assess liver function and detecting deficiencies in the extrinsic and common pathway. PT is a measure of the extrinsic pathway and assesses the time it takes for the blood to clot in vitro after added tissue factor. There are two major assays used globally. Quicks assay type, already formed in 1935 (81), is based on a preparation of rabbit brain thromboplastin (rich in tissue factor) and calcium chloride. In recent years, recombinant tissue factor has been used. The result of this assay measures the activity of the vitamin K dependent cofactors II, VII, X and of factor V and fibrinogen. Factor V is unstable and accordingly the blood sample has to be analyzed within an hour or the blood sample has to be separated and frozen. A more specific assay was described in two decades later by Paul Owren in Oslo (82, 83). This method is characterized by mixing the patient sample with thromboplastin, factor V, fibrinogen and calcium chloride. The addition of factor V and fibrinogen, often in the form factors II, VII and X depleted bovine plasma, this assay is more specific for the assessment of factors II, VII and X. The Owren method is mostly used in the Nordic and Baltic countries whereas Quicks assay is more frequently used in the rest of the world.

Before standardization of the PT the results were expressed as seconds, prothrombin index, prothrombin activity and prothrombin ratio. The standardization of the PT, the International normalized ratio (INR) was adopted by the World Health Organisation in 1983 (84). Due to variations of tissue factor in the reagents used in the different manufacturers, each manufacturer assigns an ISI value (International Sensitivity Index).

$$INR = \frac{PT}{MNPT}^{ISI}$$

PT is the prothrombin time in seconds, and MNPT is the geometric mean of PT of plasma samples from at least 20 normal subjects. The INR reference value for a patient not taking vitamin K antagonists is 0.8-1.2.

Time in therapeutic range (TTR)

VKA-therapy has mostly been studied in patients with AF. Patients with AF have a 5- to 7-fold increased risk of stroke than the general population(85), but are also associated to increased bleeding risk. The net clinical benefit of stroke reduction and bleeding risk is highly dependent on the quality of the anticoagulation treatment given. Studies have demonstrated that target range of INR 2.0-3.0 is sufficient for stroke prevention with acceptable bleeding risk (86). Guidelines recommendations are

based on the increased risk of TE when INR < 2.0 and the substantial risk of bleeding when INR > 4.0. TTR is an acceptable measure of the quality of anticoagulation therapy and the percentage of time that the patients' INR are within this range has been shown to be associated with clinical outcomes such as TE and major bleeding events (87). The definition of time in therapeutic range (TTR) in an individual is the percentage of time within the target range divided by total treatment time. The most widely used method to calculate TTR is according to Rosendaal method (88), which uses linear interpolation to assign an INR value to each day between successive observed INR values. A meta-analysis demonstrated that TTR and percentage of INRs in range were the most reported measures in studies of patients with AF to determine INR control, and that lower TTR was associated with TE and bleeding events (89). The TTR was inversely associated with adverse events (figure 9). However, very high center TTR seems not to correlate with adverse events when TTR is above 70%, at least in patients with AF (90). Studies in patients with MHV and the association of TTR with adverse events are sparse in the literature. One study showed that mortality increases at a lower quality of anticoagulation treatment in terms of frequency of PK outside the INR target range of 2.0-4.0 and did not used interpolated TTR (55). This study included patients with the Medtronic Hall valve (tilting valve disk) from 1979-1994 in a time with changing recommendations regarding target INR and before PT (%) was standardized.

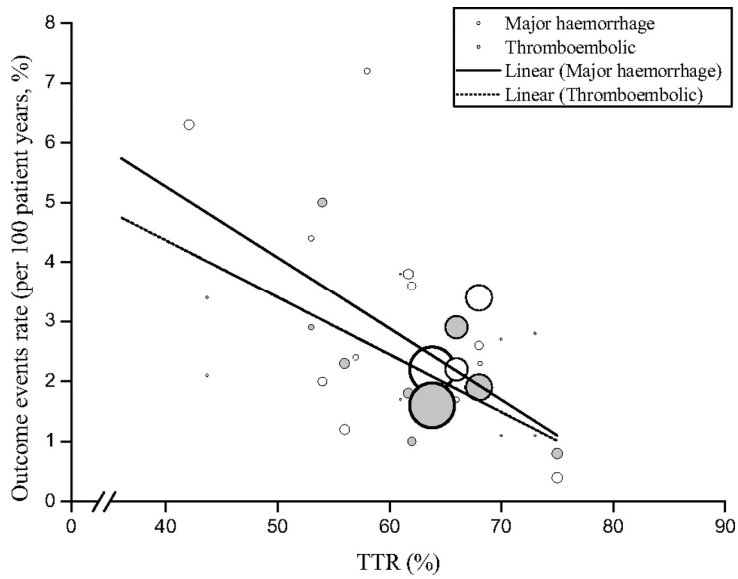
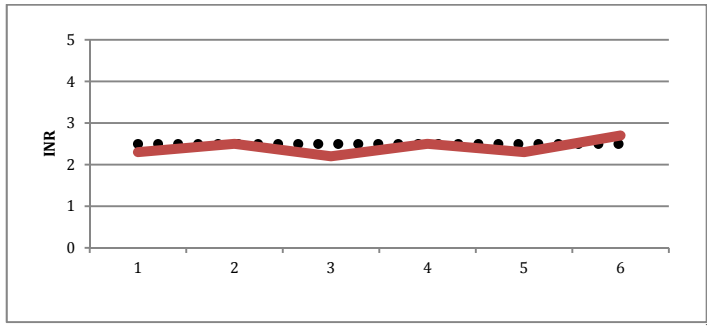


Figure 9.
TTR versus adverse events (weighted by sample size) for all studies.
Yi Wan et al. Circ Cardiovasc Qual Outcomes. 2008;1:84-91

INR variability

TTR assesses the percentage of time spent within the target range, not considering the variations of the achieved INR values within the INR target range. The effect of INR variability was initially described as variance growth rate by Fihn et al.(91) which reflected the degree to which a patient's prothrombin ratio deviated from the target prothrombin ratio over a prolonged interval. It was showed that the highest variability tertile compared to the lowest tertile was independently associated to serious bleeding. The formula of defining INR was subsequently modified by Cannegieter et al.(92) and Fihn et al.(93), which now only considered the variance of the achieved INR values and did not take account of the INR target ranges. This means that a patient is most stable with regards to INR variability when the INR values are around the same level even if the INRs are constantly above or below the limits of the target range. Example of different levels of TTR and INR variability is showed in figure 10. The modified formulas are quite similar to the standard deviation of the achieved INR values. There are studies involving patients with AF showing that INR variability predicts definitive outcomes (91, 94, 95) and one study showed that the variability predicts adverse events independent of TTR (95). van Leeuveen et al. (96) demonstrated in a case-control study in 630 patients with MHV that INR variability combined with TTR was best associated with complications. The significant hazards were obtained with a time window of three months before events occurred. The INR target range of 2.5-4.0 was used to calculate TTR despite that the INR target range of 3.6-4.8 was used at the time of the study (1985-1993) and did not adjust for other significant variables that could have affected outcomes.



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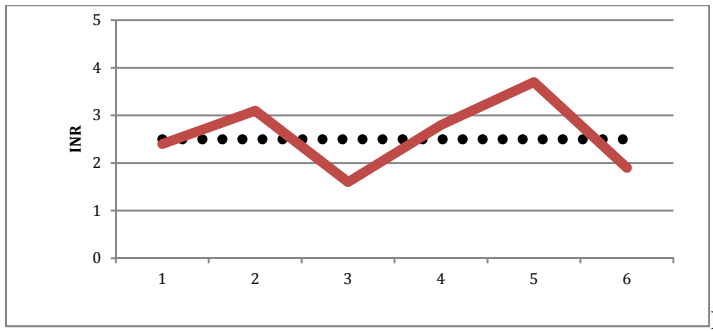

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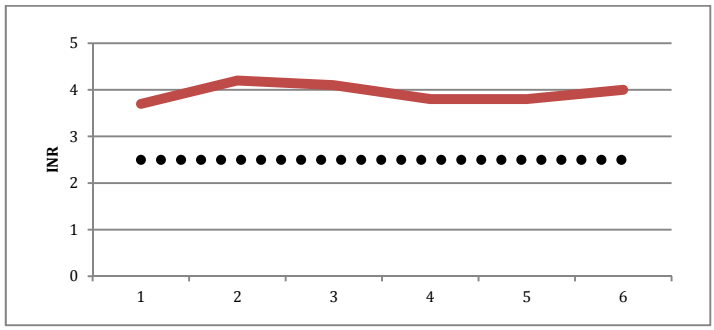


C

Figure 10.
Difference between TTR and INR variability. Black dotted line; INR target. Red line; achieved INR results. A; High TTR and low INR variability. B; Moderate TTR and high INR variabiity. C; low TTR and low INR variability.

Chronic kidney disease

Chronic kidney disease (CKD) encompasses a wide spectrum of different etiology and pathophysiologic processes that ultimately give rise to reduced kidney function and a progressive decline in glomerular filtration rate (GFR). The estimated GFR (eGFR) has been classified according to the National Kidney Foundation in five stages (CKD 1-5). Independent of the etiology of CKD, there are two broad sets of pathophysiologic mechanisms that causes the damage. Firstly, mechanisms that are specific to the underlying etiology such as immune complex deposition, inflammation, toxin exposure or genetically caused abnormalities in kidney development. Secondly, progressive mechanisms involving hyperfiltration and hypertrophy of the remaining nephrons which leads to reduction of renal mass. The most important risk factors for developing CKD are diabetes, hypertension, autoimmune disease, older age, heredity of CKD and previous episode of acute kidney injury.

In order to stage the CKD, knowledge about eGFR is necessary. The most correct methods to estimate GFR is by using urinary or plasma clearance of exogenous markers. These methods are not routinely available and needs laboratory measurements, but are considered as gold standard (plasma clearance of inulin and iohexol). Thus, clinicians rely on endogenous creatinine clearance to assess the kidney function. Plasma creatinine has however a non-linear relationship with GFR which makes it not suitable of estimating GFR when the kidney function is impaired. Plasma creatinine is highly dependent on muscle mass, diet, malnourishment, ethnicity and sex, and large differences between measured GFR and creatinine-based equations can be found. Cockcroft-Gault, the modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collabaration (CKD-EPI) are the most used creatinine-based equations. Cockcroft-Gault from 1976 uses age, sex, weight and plasma creatinine, and results in an absolute eGFR (mL/min). The MDRD-equation was introduced in 2000 with same variables as Cockcroft-Gault with the addition of ethnicity (Afro-Americans), and results in a relative eGFR (ml/min/1.73 m^2). CKD-EPI is an expansion of MDRD and introduced 2009. In comparison to plasma creatinine, cystatin C is relatively independent muscle mass/body composition. Thus, there are cystatin C-based equations for GFR that consists of only cystatin C and age. The mean value of eGFR based on both creatinine and cystatin C is more accurate than the equations based on either. This

applies specially to patients with reduced GFR. The revised Lund-Malmö equation (LM rev), derived and internally validated locally, has two age terms with opposite signs, which possibly handles expected changes in GFR across the life span better. The LM rev equation performed better than MDRD and CKD-EPI across GFR, age and BMI intervals (97, 98).

A systematic review by the Swedish Council on Health Technology Assessment (SBU) was made in 2013 and assessed all studies estimating the kidney function (99). In usual practice, an eGFR equation is suitable for clinical use if at least 75% of the estimates fall within ±30% of the measured GFR. The accuracy of MDRD was 81% and for CKD-EPI 84%. The difference between these equations is explained mostly by MDRDs underestimation of GFR in patients with normal GFR. The LM rev equation has higher accuracy in patients with eGFR <30 ml/min/1.73 m^2 compared to MDRD and CKD-EPI, similar accuracy as MDRD but higher than CKD-EPI in eGFR 30-90 ml/min/1.73 m^2. For eGFR >90 ml/min/1.73 m^2 CKD-EPI has higher accuracy than LM rev and MDRD. It should be emphasized that the LM rev has been validated externally only once.

Cardiovascular disease is the leading cause of morbidity and mortality in patients with CKD worldwide. The crude risk of cardiovascular disease in patients with CKD compared to age- and sex matched general population ranges from 10-200-fold. Adjusted risk of mortality, cardiovascular events and hospitalization increases inversely with eGFR in the general population (100). Ischemic vascular disease is common in CKD and derives both from the traditional risk factors as hypertension, hypervolemia, dyslipidemia and sympathetic overactivity, but also from CKD-derived variables. These include anemia, hyperphosphatemia, hyperparathyroidism, sleep apnea and generalized inflammation. Patients with CKD have paradoxically increased risk of thrombosis and bleeding due to altered hemostasis. Patients with severe renal impairment are at increased risk of thrombosis due to different platelet and coagulation abnormalities, such as endothelial damage, alteration in protein C metabolism, defects in the expression of glycoprotein Ib and elevated plasminogen activator inhibitor-1 to tissue-type plasminogen activator ratios (101). There are numbers of pathophysiological mechanisms and interactions between heart disease and CKD. Often is this interaction bidirectional. The neurohormonal adaption and activation of renin-angiotensin-aldosterone system leads to volume overload and results in ventricular hypertrophy and eventually to heart failure. Hypertension is one of the most common complications of CKD and interacts also with the development of heart failure.

There are no publications regarding patients with CKD stage 3-4 (eGFR 15-60 ml/min/1.73 m^2) and MHV. There are however some retrospective studies in patients with CKD stage 5 (eGFR <15 ml/min/1.73 m^2) and MHV studying outcomes. Herzog et al (102)showed in a large retrospective study involving patients in dialysis

from 70s-90s that the mortality between bioprosthesis and MHV were not significantly different. Due to the need of VKA therapy in patients with MHV and the multiple increased risk of bleeding and smaller retrospective studies (103, 104), guidelines favors bioprosthesis than MHV in patients with end-stage renal disease, despite the accelerated structural valve deterioration in patients with bioprosthesis and end-stage renal disease.

Aims of the thesis

Paper I: To report incidence of thromboembolism, major bleeding and mortality in all patients with mechanical heart valve prosthesis in two centers, and to identify risk factors for these adverse events and mortality. Furthermore, we sought to compare the mortality risk in the general population without MHV.

Paper II: To investigate the incidence of thromboembolism, major bleeding and mortality and the combined endpoint of these outcomes, in relation to eGFR in patients with MHV.

Paper III: To investigate the effect of INR variability on thromboembolism, major bleeding and mortality, and if using INR variability and TTR can predict the combined endpoint more accurately. Furthermore we sought to determine the INR at the time of the adverse event within designated TTR levels to evaluate the most optimal anticoagulation intensity.

Paper IV: To report incidence and to identify risk factors for thromboembolism and major bleeding in patients with MHV in a nationwide population-based study, and to validate the results from paper I.

Materials and method

Paper I-III

Population and cohort descriptions

The cohort used for paper I-II is based on all patients on VKA therapy for the indication MHV at two centers in Sweden, Skåne University Hospital in Malmö and Sundsvall Hospital. Skåne University Hospital in Malmö serves more than 300,000 inhabitants and is one of the largest emergency departments in Sweden in terms of patients. Sundsvall Hospital is a county hospital located in the central part of the country and serves approximately 150,000 inhabitants. Auricula is the Swedish national quality register for AF and oral anticoagulation and was founded in 2006. There are currently 224 active centers with approximately 122,000 patients on VKA treatment that are managed in Auricula (105). This corresponds to about half of the Swedish Warfarin population. It is a web-based system and provides a clinical decision tool and aids in the dosage of warfarin using a dosing algorithm. This register contains key patient characteristics such as age, sex and specific Swedish personal identity number. Further, information on risk factors for thromboembolism and major bleeding is registered, concurrent illnesses, current treatment and indication of VKA treatment. When using the dosage system, quality parameters are automatically registered. Key outcome measures are thromboembolism and major bleeding, and are requested annually, as well as the end of each treatment period.

For paper I and II, all patients with VKA treatment and the indication MHV from Skåne University Hospital in Malmö and Sundsvall Hospital in Auricula were followed during the study period 01/01/2008 – 12/31/2011. During the study period, patients in Malmö had an INR target of 2.0-4.0 for all patients with MHV irrespective of valve position. Patients in Sundsvall had an INR target of 2.0-3.0 for AVR and 2.5-3.5 for patients with MVR or combined valve prosthesis. For paper III, only patients from Malmö for the same period were included. All patients with ongoing VKA therapy irrespective of date of valve surgery were included, and with enrollment of patients that received the valve replacement during the study period.

TE was defined according to the guidelines for reporting mortality and morbidity after cardiac valve surgery (106), i.e. stroke, transient ischemic attack (TIA) or an embolus documented operatively, at autopsy, or clinically that produces signs or symptoms attributable to complete or partial obstruction of a peripheral artery. The major bleeding events were defined according to ISTH (International Society on Thrombosis and Haemostasis) (107). This included falls in haemoglobin levels of greater than 20 g/L, transfusion of ≥2 units, symptomatic bleeding in a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, as well as intramuscular with compartment syndrome) or fatal bleeding. The bleeding definition of ISTH is very similar to the definition in the guidelines for cardiac surgery, and was chosen due to its comprehensive use since publication.

All events of TE and major bleeding were retrospectively validated at each center by one of the authors and evaluated if the strict definition of TE and major bleeding were fulfilled. The cause of mortality was most often registered in the medical records or Auricula, but for those patients that this information was missing, the Swedish Cause of death register was used. The definition of valve-related mortality and cardiac death was taken from the guidelines for reporting mortality and morbidity after cardiac valve surgery (106). Informed consent was obtained from all participants, and the regional ethical review board in Lund approved the studies. The study protocol is consistent with the principles of the Declaration of Helsinki.

Kidney function

For paper II, kidney function was measured by obtaining all plasma creatinine values from the centers during the study period. A mean value was used to estimate the GFR by the revised Malmö-Lund equation without body weight measure (108). This formula is derived and internally validated in the present Skåne University Hospital. The GFR was also estimated with MDRD and CKD-EPI for comparison. The ethnicity was however not considered in the formula of MDRD equation since we did not have information about the ethnicity of the patients. Patients were presented in pre-specified subgroups according to the international classification of CKD-stages. These strata were eGFR <30, 30-45, 45-60 and >60. Due to insufficient data on plasma creatinine in 26 patients (4.7%), these patients were excluded in the study, resulting in 520 patients.

Revised Malmö-Lund formula without body weight measure (pCr in µmol/L):

$e^{x\text{-}0.0158xage+0.438xln(age)}$

Female and pCr <150: X=2.50 + 0.0121 x (150-pCr)

Female and pCr ≥150: X=2.50 - 0.926 x ln(pCr/150)

Male and pCr <180: X= 2.56 + 0.00968 x (180-pCr)

Male and pCr ≥180: X= 2.56 - 0.926 x ln(pCr/180)

INR analysis

All INR values were obtained from Auricula. The INR variability was calculated using Fihn's modified method that estimates the degree to which a patient's INR deviates from the previous one, not taking the INR target into consideration.(93) This equation is very similar to the standard deviation equation. Patients that had fewer than 5 INR samples in the cohort were excluded from the analysis due to the risk of overestimating the variability when INR samples are few. Patients that discontinued warfarin due to end-stage diseases despite presence of MHV were also excluded. All INR samples were included until the day of the event, thus all INR samples following an event were excluded due to the risk of dilution of results. Hence, for each patient that was included a variability score was calculated for.

Variance growth rate by Fihn's method (INR variability).

$$\sigma^2 = \frac{1}{n-1}\sum_{i=1}^{n}\frac{(INR_{i+1} - INR_i)^2}{\tau_i}$$

TTR was calculated according to Rosendaal method with interpolation for the different INR ranges(88).

Propensity score method

Randomized controlled trials are considered to be the gold standard approach for estimating effect of treatment, exposure or interventions between groups. The purpose of allocating participants randomly ensures that treatment status will not be confounded with either measured or unmeasured baseline characteristics. When dealing with observational cohorts, treatment selection is often influenced by subject characteristics, which make comparisons complicated. To account for systematic differences between treated and untreated subjects, propensity score methods can be applied to mimic some of the characteristics of a randomized controlled trial. The

propensity score matching (PSM) is a tool to adjust a treatment effect for measured confounders in observational cohorts. The propensity score is a balancing score, and is defined as the probability of receiving treatment based on measured covariates. For instance, in a cohort all of whom have the same propensity score, the distribution of observed covariates will be similar between the groups (109). The propensity score is often estimated by using logistic regression in which the treatment assignment is used as the outcome variable, and the selected covariates as predictors. The matching process can be made in several different ways (110). Matching can be made with or without replacement, which means that selected and matched subjects availability for new matches is decided upon. Another choice is between greedy and optimal matching. Optimal matching in which matches are formed so as to minimize the total within-pair difference of the propensity score, whereas in greedy matching an untreated subject is whose propensity score is closest to that of the randomly selected treated subject is chosen. Matching can be performed in which a specified number of control units can be matched to a single treatment unit, e.g. 2:1 or 3:1 ratio matching. There are two primary methods to select the criteria for nearest neighbor matching. Nearest neighbor matching, matches a given treated subject with an untreated subject whose propensity score is "close" to the treated subject. Nearest neighbor matching within a specified caliper distance is similar to the aforementioned method with the restriction that the difference between the matched subjects must be below some pre-specified threshold (the caliper distance). This method can prevent "bad" matches where the covariates are likely to be imbalanced. After matching is completed, standardized mean differences and the variance ratio can be tested for to check for if balance has been achieved. The PSM is written in R, which is a free software environment for statistical computing and graphics. The program "psmatching" is written as a custom dialog in SPSS and works with SPSS versions 18 and upward (110).

PSM were made for paper I and IV, but were not included in the published articles. For paper I, our aim was to compare the different INR target ranges that existed between the cohorts in Malmö (INR 2.0-4.0 for all valves) and Sundsvall (INR 2.0-3.0 for AVR and 2.5-3.5 for MVR). Given the older and greater comorbidity in the Malmö cohort compared to the Sundsvall cohort, PSM were made to compare the incidence of the new matched cohort.

Paper IV

This study ranged from 01/01/2006 – 12/31/2011 and involved all patients on VKA treatment with MHV that were registered in Auricula in Sweden. Following extraction of patients and data from Auricula, the study cohort was created by merging data from with the National Patient Registry (NPR) and the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry. The NPR has published statistics and surgical treatment for more than 100 years in Sweden. It contains data on patient characteristics and covers all diagnoses recorded in the patient's medical records within hospitals in Sweden, for outpatient as well as inpatient care. It does however not cover primary care. SWEDEHEART includes almost all patients admitted to a Swedish CCU or other specialized wards that care for patients with acute coronary syndrome (ACS). It was launched in 2009 after merging with different Swedish national registries (RIKS-HIA, SCAAR, SEPHIA and the Swedish Heart Surgery registry). The registry prospectively registers information for 106 variables in patients admitted to hospital because of symptoms suggestive of ACS. One if its components, the Swedish Heart Surgery registry cover information on approximately 7,000 patients undergoing heart surgery annually and captures nearly 100% of the patients, and include details on patient background and surgical procedures.(111)

Each treatment period in Auricula was given an individual identification number. Within the study period, patients could have more than one treatment period, depending on a new indication for warfarin treatment. For instance, a patient with an AVR that receives an MVR during the study period will obtain a new treatment period. For patients that started or continued after the study period, start and end dates were set to the study's start and end dates. We defined TE and major bleeding according to predefined ICD-10 codes. Time was calculated until a first complication of every specified type (TE or major bleeding). In order to reduce the risk of overrating the complications we allowed only one of every subtype per treatment period. This implies that a treatment period could have only one gastrointestinal bleeding, one intracranial bleeding and one stroke. Hence, the rate was defined as the firsts major bleeding or stroke/TE, or the total of every subtype of that endpoint.

There were some patients (n=358) underwent heart surgery between in a time where ICD-9 codes were used (before 1998). Consequently, we did not have access to preoperative risk factors for these patients. There were additionally 37 patients that had no preoperative diagnose codes registered in ICD-10. All of these patients were excluded in the multivariate analysis in order to reduce the risk of dilution of results and patient characteristics, but was however included in the analysis of rate of complications. The mortality was excluded during the index hospitalization, due to

the fact that these patients were not admitted to an anticoagulation clinic for inclusion in Auricula and escaped registration. Thus, 30-day mortality was not reported.

Statistics

Paper I

Categorical data were reported by percentages and normally distributed data were presented as mean with standard deviations. TTR was calculated according to Roosendaal's algorithm with linear interpolation (88). The rates of complications were reported as incidence per 100-patients years, using the Person Time module in OpenEpi, version 2.3.3 (www.openepi.com). The comparisons of rate were made by Mid-P exact test and performed two-tailed, and a p-value <0.05 were considered significant. Univariate and multivariate logistic regression analysis with all the included variables was used to identify risk factors associated to TE and major bleeding. Cox proportional-hazard regression models for survival analysis were made, using time since valve replacement as the time variable. In order to compare the mortality and acute myocardial infarction (AMI) rate between our cohort and general population, standardized mortality/morbidity ratios were calculated. Age- and sex-specific rates of 5 years in the general population of Malmö and Sundsvall were calculated, and compared with the study population. If the ratio of observed/expected death/AMI is greater than 1.0, there is a hazard of excess death/AMI in the study population. Analyses were performed using SPSS statistics (version 21; SPSS Inc, IBM Corporation, NY).

Paper II

Patient characteristics was reported according to prespecified subgroups defined by eGFR strata of < 30, 30-45, 45-60 and > 60 ml/min/1.73m^2. Univariate analysis with the different endpoints and the combined endpoints were reported for the association of eGFR as a continuous variable. Statistical significant covariates for the different endpoints were included in the multivariate analysis, and adjusted cox regression models were then estimated for association to eGFR. The incidence of the combined endpoint per 100 patient-years and the relation to eGFR strata were then reported for the crude and adjusted risk, with eGFR >60 ml/min/1.73m^2 as the reference. Analyses

were performed using SPSS statistics (version 22; SPSS, Inc IBM Corporation, Armonk, NY).

Paper III

INR variability was calculated according to the modified version of Fihn's which considers pure INR variability(93). Due to skewed distributions of INR variability, it was logarithmically transformed to minimize influence of extreme observations and in order to compare the variable with TTR. The linear relationship between log INR variability and TTR was estimated by the Pearson correlation coefficient value. Log INR variability and TTR were then separately analyzed in a cox proportional-hazards regression model to investigate the association with the different endpoints. The beta coefficient expressed per one standard deviation increase of each factor was made to allow comparison between the independent variables. Significant covariates in the univariate analysis were included in the multivariate analysis.

In order to investigate the cutoff point where the log INR variability is becoming significantly associated with the endpoints, a crude cox regression model was formed by dividing the log INR variability into five quintiles with the lowest quintile as the reference. This produced a cutoff point <-0.43 based on the fourth quintile where the combined endpoint was nearly significantly increased compared to the lowest quintile. This cutoff point could subsequently be calculated in the following analyses as the breakpoint of high and low log INR variability. To investigate both measures of INR variability and TTR, an age-adjusted cox regression model for the different endpoints was formed where high and low variability within different levels of TTR was calculated, with high TTR/low variability as the reference group that theoretically would be associated with the lowest risk of complications. The TTR of 2.0-4-0 was divided into three tertiles based on the distribution of the cohort which consisted of TTR (<89.1%,89.1-96.0%, >96%).

The distribution of time spent within designated INR ranges of 0.5 was estimated, and INR measurements at the time of an event were collected to calculate the incidence rates of TE and major bleeding for each designated INR interval. The incidence rates were then plotted against the designated INR intervals. Analyses were performed using SPSS statistics (version 22; SPSS Inc, IBM Corporation, Armonk, NY).

Paper IV

Incidence rates are reported per 100 treatment-years with appropriate confidence intervals of 95%, and time contributed within each age span of 10 years were calculated with the patient's age at the time of the event. Univariate analysis were made for all the preoperative covariates and significant covariates (besides age and sex), and important risk factors that with known association to the outcomes were included in the multivariate cox regression model. For TE, associated risk factors that were included although they were not significant in the univariate analysis were hypertension, AF, heart failure, kidney failure and vascular disease. For major bleeding, risk factors that comprise the HAS-BLED score were included. These include hypertension, kidney failure, alcohol overconsumption, liver failure, previous stroke and major bleeding. Since all the patients had different date for valve surgery, time since valve replacement were included for both analysis. For mortality, all covariates were significant in the univariate analysis and thus included in the multivariate analysis. Using all preoperative variables as covariates (table 1) and using patients <60 years and <65 years as the dependent variable, propensity score was calculated for each patient in two different cohorts. A propensity score matched cohort was constructed by 1:1 and 1:2 nearest neighbor matching of under and over the threshold, without replacement. A caliper width of 0.2 of the SD of the logit of the propensity score was used. Following the matching procedure standardized differences for variables were calculated to investigate post-match balance. Balance was defined as standardized mean differences of the covariates <0.25 after matching. In the propensity-matched cohorts, the risk of TE, major bleeding, and a combined endpoint of these outcomes were assessed in relation to the age categories in a Cox regression model with only the age category as the covariate. Statistical analyses were calculated with SPSS Statistics (version 22.0; SPSS, Inc, IBM Corporation, Armonk, NY), R version 3.1.14, R Foundation for statistical Computing, Vienna, Austria. URL http://www.R-project.org/ and the Person Time module in OpenEpi, version 3.03a (www.openepi.com).

Results

Paper I

There were a total of 546 patients in the cohort, 398 patients with AVR, 122 patients with MVR and 26 patients with combined AVR/MVR. There were 407 patients in Malmö with the INR target range of 2.0-4.0, and 139 patients in Sundsvall with INR target range of 2.0-3.0 for AVR and 2.5-3.5 for MVR. The patients in Malmö were significantly older (mean 70 vs. 61), had more vascular disease (4% vs. 1%), previous major bleeding (13% vs. 4%), females (43% vs. 25%), heart failure (32% vs. 17%) and MVR (27% vs. 9%) than the cohort in Sundsvall. There were some differences between the AVR and MVR group. The proportion of females was higher in the MVR group (53% vs. 31%), AF (66% vs. 28%), heart failure (39% vs. 25%) and previous stroke (17% vs. 11%) than the AVR group.

Events

The TE-events that occurred during the study period consisted of 1 valve thrombosis, 3 peripheral embolisms, 32 stroke/TIA as presented in table. Patients with AVR had an incidence of 1.8 per 100 patient-years whereas patients with MVR had 2.2 per 100 patient-years, p =0.6. No statistical difference was found between patients that were enrolled during the study period (n=75) and patients that received the valve replacement before the study period.

A total of 81 major bleeding events occurred for 77 patients during the period. The incidence for patients with AVR and MVR was 4.4 and 4.6 per 100 patient-years respectively, p= 0.7. The most common sites of major bleeding were gastrointestinal and of other origin.

Eighty-five patients died during the period. Twelve (14%) were valve-related and 42 (49%) cardiac-related. The valve-related deaths were two gastrointestinal fatal bleedings, two intracerebral bleedings, two ruptures of aortic aneurysms, one subdural bleeding, one aortic dissection, one severe chronic iron deficiency anemia and three ischemic strokes.

Table 4.
Patient charecterstics before and after propensity score matching.

	Before propensity		Propensity matched		
	Malmö	**Sundsvall**	**Malmö**	**Sundsvall**	**SMD [e]**
Patient (n)	407	139	181	108	
Age	70.1 (±14.1)	61.5 (±13.6)	65.0 (±13.5)	62.7 (±13.3)	0.17
Female	173 (43)	34 (25)	52 (29)	29 (27)	0.04
Time since valve replacement	8.4 (7.1)	6.6 (6.7)	7.4 (7.5)	6.6 (7.0)	0.11
Aortic valve replacement	279 (72)	119 (90)	137 (76)	91 (84)	0.22
Mitral valve replacement	109 (28)	13 (10)	37 (20)	10 (9)	0.32
Aortic and mitral valve replacement	19 (5)	7 (5)	7 (4)	7 (7)	0.12
Hypertension	245 (60)	103 (74)	125 (62)	76 (70)	0.03
Diabetes	60 (15)	16 (12)	25 (14)	14 (13)	0.03
Previous stroke/TIA	52 (13)	14 (10)	17 (9)	11 (10)	0.03
Previous venous TE	10 (3)	0 (0)	1(1)	0(0)	-
Vascular disease [a]	17 (4)	1 (0.7)	3 (2)	1 (1)	0.07
Previous bleeding	51 (13)	6 (4)	13 (7)	5(5)	0.11
Previous AMI	75 (18)	8 (6)	11 (6)	6 (6)	0.02
Alcohol overconsumption [b]	10 (3)	1 (1)	2 (1)	1 (1)	0.02
Antiplatelet drugs	12 (3)	0 (0)	2 (1)	0(0)	-
eGFR	62.3 (19.1)	71.4 (22.5)	69.1 (17.1)	70.1 (23.4)	0.05
Liver failure [c]	3 (1)	4 (3)	3 (2)	0(0)	0.18
Atrial fibrillation	161 (40)	51 (37)	69 (38)	38 (35)	0.06
Paroxysmal	57 (14)	13 (9)	28 (16)	11 (10)	
Permanent	104 (26)	38 (27)	41 (23)	27 (25)	
Heart failure	130 (32)	24 (17)	39 (22)	18 (17)	0.12
LVEF [d] (35-50%)	110 (27)	22 (16)	32 (18)	18 (17)	
LVEF (<35%)	20 (5)	2 (1)	7 (4)	0 (0)	

Values are presented as mean ± SD or n (%). [a] Peripheral arterial disease or aortic plaque ; [b] ≥ 8 Units/week; [c] Chronic hepatic disease or bilirubin > x 2 upper limit of normal in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase > x 3 upper limit of normal; [d] Left ventricle ejection fraction; [e] standardized mean difference between the groups in the propensity matched cohort

Tabel 5.
Incidence rates and hazard ratios before and after propensity score matching.

	Before propensity score match			
	Malmö	**Sundsvall**	**HR (95% CI)**	**P-value**
TE	1.93 (1.29-2.79)	1.41 (0.62-2.79)	0.74 (0.32-1.69)	0.47
Bleeding	5.15 (4.02-6.5)	1.81 (0.88-3.32)	0.36 (0.18-0.72)	0.004
MI	1.38 (0.85-2.11)	0.59 (0.15-1.61)	0.44 (0.13-1.47)	0.18
Death	5.04 (3.96-6.33)	2.92 (1.70-4.71)	0.57 (0.33-0.998)	0.049
	Propensity score matched			
	Malmö	**Sundsvall**	**HR (95% CI)**	**P-value**
TE	2.12 (1.18-3.54)	1.57 (0.64-3.26)	0.74 (0.28-1.9)	0.54
Bleeding	4.18 (2.77-6.08)	2.07 (0.96-3.94)	0.52 (0.23-1.15)	0.11
MI	0.95 (0.39-1.98)	0.77 (0.19-2.08)	0.82 (0.20-3.27)	0.76
Death	3.41 (2.19-5.08)	3.01 (1.63-5.11)	0.86 (0.43-1.74)	0.68

Incidence rate per 100 patient-years; TE, thromboembolism; MI, myocardial infarction.

Propensity score matching

In order to balance out the differences in the patient characteristics between the cohorts in Malmö and Sundsvall, propensity score matching was made. The PSM cohort yielded 181 patients in Malmö and 108 patients in Sundsvall with balanced covariates, measured by standardized mean difference (all <0.10) except for higher proportion of MVR in the Malmö cohort (20% vs. 9%), table 4. The cohort before propensity score matching demonstrates a significant increased risk of major bleeding and death in the Malmö cohort, whereas the risk of TE and AMI are non-significantly increased, table. Following PSM, the incidence of major bleeding was still doubled compared to the Sundsvall cohort, however not significantly increased (p=0.11). There was a slightly increased non-significant risk of TE and death in Malmö as presented in table 5.

Multivariate analysis

Few of the variables were significant in the univariate analysis for TE and major bleeding. For TE, only vascular disease emerged as a significant risk factor, odds ratio (OR) 4.2 (95% CI 1.02-17.4). AF, heart failure, kidney failure and previous stroke did not show any trends towards association to TE in the univariate analysis. The logistic regression analysis was adjusted for all the variables listed in table 4, due to

stated association to TE from other settings in patients with oral anticoagulation treatment. A different logistic regression model was made with the dependent variable being TE with the addition of AMI, du to clinical relevance of this endpoint. Heart failure OR: 2.2; (95% CI: 1.2-4.8), previous AMI OR: 2.2 (95% CI: 1.1-4.6) and vascular disease OR: 3.9 (95%: 1.2-12.4) emerged as independent risk factors for TE and AMI.

Variables that were significant in the univariate analysis for major bleeding were age >75 years, hypertension, heart failure, previous bleeding, previous AMI, alcohol overconsumption, NSAID/antiplatelet agents use and kidney failure. Only previous major bleeding OR: 2.8 (95% CI: 1.4-5.6) emerged as an independent risk factor, with age >75 OR: 1.7 (95% CI: 0.97-3.10; p =0.06) and alcohol overconsumption OR: 3.6 (95% CI: 0.91-14.5; p =0.07) showed a considerable trend toward significance.

A cox proportional hazard model was estimated for mortality adjusted for variables that were significant in the univariate analysis and presented in table. Valve position was not however significant in this analyze, but included in the multivariate analysis due to known increased risk of adverse events in MVR.

Standard mortality/morbidity ratio

A total of 1,359,769 person-years were gathered from Statistics Sweden, from the inhabitants from the regions Malmö and Sweden. The expected age- and sex-specific rates of 5 years of death and AMI were calculated and compared to the present cohort. The standard mortality/morbidity ratios were 0.99 (95% CI: 0.8-1.2) and 0.87 (95% CI: 0.5-1.2) for mortality and acute myocardial infarction respectively.

Paper II

A total of 520 patients were included in the cohort with a total of 1,813 patient-years of follow-up time. Twenty-six patients had insufficient data on plasma creatinine and were excluded in the analysis. Baseline characteristics are presented according to the different eGFR strata of <30, 30-45, 45-60 and >60 ml/min/1.73m^2. Mean age had an increasing trend with decreasing eGFR strata, 62, 76, 83 and 83 years respectively. Hypertension, diabetes, AF, heart failure and previous stroke and bleeding events were all more common with decreasing eGFR strata (p <0.001 for trend). The adjusted mean TTR of 2.0-3.0 and 2.0-4.0 decreased with each decreasing eGFR stratum, as well as the proportion of % of INR >3.0 and >4.0, $CHA_2DS\text{-}VAS_2c$ and HAS-BLED score.

Table 6.
Patient characteristics stratified according to eGFR.

eGFR strata, ml/min/1.73 m^2					
n (%)	**All**	**>60**	**45-60**	**30-45**	**<30**
n	520	330	96	61	33
Age (yrs)	69 (±14)	62 (±12)	76 (±12)	83 (±9)	83 (±9)
Male	320 (62)	219 (66)	56 (58)	30 (49)	15 (46)
AVR	376 (72)	250 (76)	61 (64)	44 (72)	21 (64)
MVR	118 (23)	63 (19)	32 (33)	14 (23)	9 (27)
AVR/MVR	26 (5)	17 (5)	3 (3)	3 (5)	3 (9)
Hypertension	332 (64)	188 (57)	73 (76)	44 (72)	27 (82)
Diabetes	76 (15)	37 (11)	15 (16)	14 (23)	10 (30)
Previous stroke	65 (13)	23 (7)	17 (18)	16 (26)	9 (27)
Previous bleeding	56 (11)	19 (6)	16 (17)	12 (20)	9 (27)
Vascular disease	18 (3)	5 (2)	7 (7)	2 (3)	4 (12)
Antiplatelet agent	12 (2)	6 (2)	5 (5)	1 (2)	0
Atrial fibrillation	204 (39)	105 (32)	48 (50)	32 (53)	19 (58)
Heart failure	150 (29)	71 (22)	30 (31)	28 (46)	21 (64)
LVEF 35-50%	128 (25)	61 (19)	25 (26)	24 (39)	18 (55)
LVEF <35%	22 (4)	10 (3)	5 (5)	4 (7)	3 (9)
eGFR	63.9 (±20.3)	76.3 (±11.8)	52.7 (±4.3)	38.0 (±4.6)	20.9 (±5.5)
CHA_2DS_2-VASc	2.93 (±1.52)	2.40 (±1.36)	3.5 (±1.35)	4.02 (±1.36)	4.45 (±1.0)
HAS-BLED	1.30 (±0.85)	1.03 (±0.72)	1.53 (±0.79)	1.79 (±0.82)	2.39 (±0.83)
INR	2.80	2.76	2.84	2.89	2.88
TTR 2.0-3.0	65.6	67.5	65.0	60.3	58.1
TTR 2.0-4.0	90.7	91.4	91.3	88.8	87.2
% of INR >4.0	7.3	6.2	8.0	9.5	11.6
% of INR >3.0	34	36.8	37.8	39	34

Values are expressed as n(%) or means ± SD.

Effect of eGFR on events

Crude risk of TE, major bleeding, death and a combined endpoint of eGFR as a continuous variable were estimated in figure 11. The rates of major bleeding and death increased substantially for each decreasing eGFR stratum, without a clear

association with TE. There was a significant invers relationship between eGFR and major bleeding, death and the combined endpoint but not for TE. After multivariate adjustment for significant covariates, the same hard endpoints were significantly associated to eGFR such that every unit decrease in eGFR increased the risk of major bleeding by 2%, death by 3% and the combined endpoint by 1%, table 7.

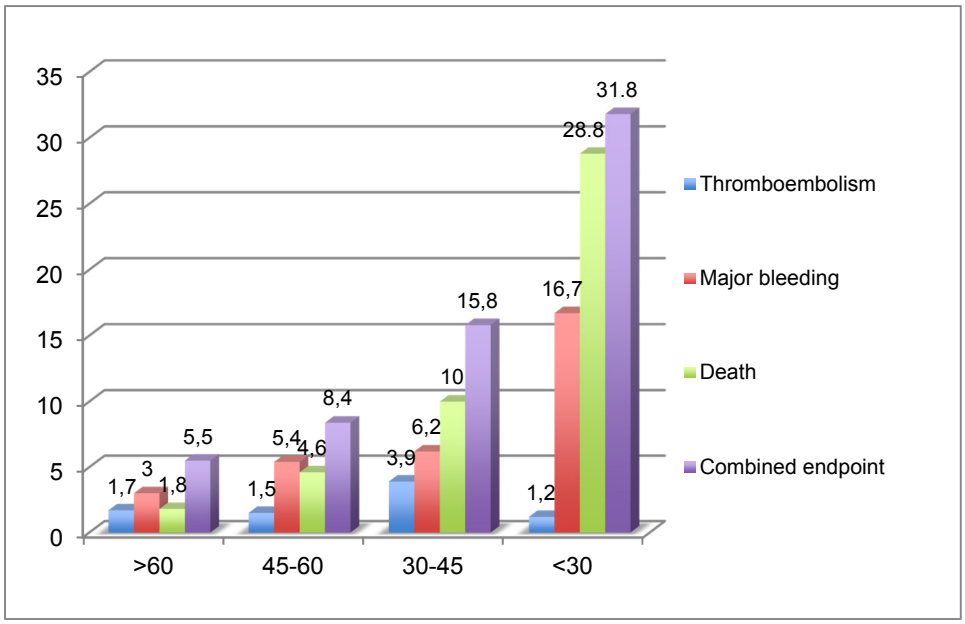


Figure 11.
Incidence rate per 100 patient-years

As there was a correlation between eGFR as a continuous variable and the combined endpoint, subgroups of the eGFR according to the CKD stages were made with eGFR >60 ml/min/1.73m^2 as the reference group. Crude risks of the combined endpoint <30, 30-45 and 45-60 ml/min/1.73m^2 compared to the reference group >60 ml/min/1.73m^2 were HR: 7.4 (4.7-11.6), HR: 3.1 (2.0-4.8) and HR: 1.6 (1.0-2.4) respectively. Adjusted hazard ratios were estimated and adjusted for age, hypertension, diabetes mellitus, heart failure, concomitant antiplatelet agent and time since valve replacement. The adjusted risks of the combined endpoint for eGFR <30, 30-45 and 45-60 ml/min/1.73m^2 compared to the reference group >60 ml/min/1.73m^2 were HR: 3.2 (1.8-5.6), HR: 1.5 (0.9-2.5), HR: 0.9 (0.6-1.5) respectively.

Table 7.
Crude and adjusted hazards of eGFR as a continous variable on outcomes.

Univariate	Hazard Ratio	(95% CI)	p-value
Thromboembolism	1.00	0.98-1.02	0.75
Major Bleeding	0.97	0.96-0.98	<0.001
Death	0.95	0.94-0.96	<0.001
Combined endpoint	0.97	0.96-0.98	<0.001
Multivariate			
Major bleeding [a]	0.98	0.96-0.99	0.005
Death [b]	0.97	0.96-0.99	<0.001
Combined endpoint [c]	0.99	0.97-0.997	0.014

Paper III

The Malmö cohort consisted of 407 patients where 13 patients had insufficient number of INR values to assess TTR and INR variability, which yielded 394 patients. The achieved mean TTR was 2.85(±0.25) for AVR and 2.89(±0.22) for MVR. TTR 2.0-4.0 was 90.9% for all the patients. During the period, a total of 18,852 INR values were obtained from Auricula to assess the anticoagulation treatment, and 1,348 patient-years of follow-up time.

Events

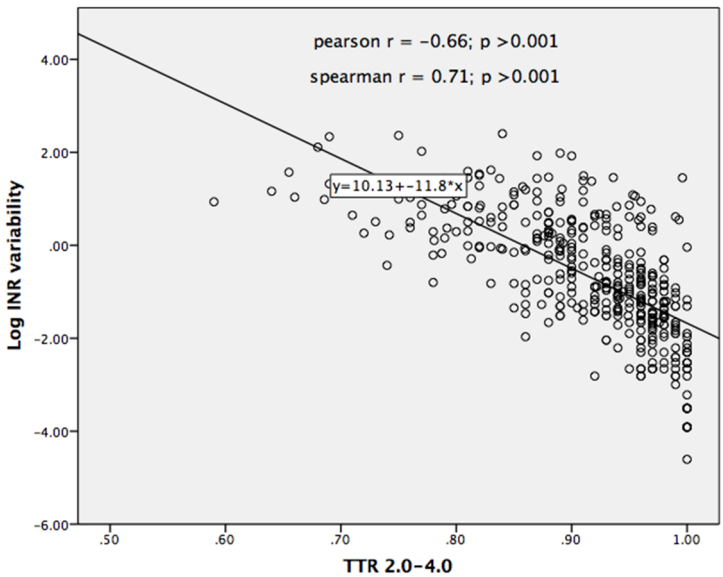
There were a total of 26 TE-events, 62 major bleeding events, and 68 deaths with a combined endpoint of 122 cases occurring during the period. Some of the events occurred during low molecular weigh heparin (LMWH) treatment; 5 major bleeding and 4 TE-events. Two patients suffered events abroad where an INR at the time of event could no be obtained and one event where an INR value was not analyzed the first day of hospitalization. These events were excluded in the specific analyzes for INR at the time of event.

Characteristics of TTR and INR variability

In order to perform some of the analysis where INR variability needs to be dichotomized, a cutoff point needed to be determined. Log INR variability was divided into five equal quintiles where the incidences of the endpoints were examined. Hazard ratios with the first quintile (lowest variability) as reference were estimated, and resulted in significant increased risk for the combined endpoint for the 5th quintile, HR: 2.6 (95% CI: 1.5-4.6) and a borderline significant trend to significance for the 4th quintile, HR: 1.6 (95% CI: 0.9-2.9). Thus, the cutoff point

were determined as log INR variability values based on the 5th, >-0.43. The TTR 2.0-4.0 decreased with increasing quintile and a clear trend of increasing risk of the different endpoint were seen, least for TE-events.

The TTR of 2.0-4.0 were divided into three tertiles of <89.1%, 89.1%-96.0% and >96.0%. A Pearson and Spearman correlation coefficient were estimated between TTR 2.0-4.0 and log INR variability. Since the association seemed to correlate but not at a constant rate in a scatterplot, both coefficients were estimated as presented in figure 12. Four obvious outliers were identified in the scatterplot and removed. The Pearson correlation was -0.57 (p <0.001) before removal and -0.66 (p <0.001) following removal.



Figur 12.
Scatterplot presenting the relationship between log INR variability and TTR 2.0-4.0 with Pearson and Spearman correlations coefficients, following removal of 4 outliers.

Effect of INR variability and TTR

The log INR variability and TTR 2.0-4.0 were separately analyzed in an adjusted cox regression analysis with the beta coefficient expressed per one standard deviation (SD) increase of each independent variable to allow comparisons. The endpoints were adjusted for significant risk factors presented in table 8. There was a similar association between the combined endpoint and log INR variability, and to TTR 2.0-4.0 of 30% increase and 29% decrease for each variable respectively. Log INR variability was significantly associated to TE whereas TTR 2.0-4.0 was not. For major

bleeding events, there was a significant association with TTR 2.0-4.0, which log INR variability was not associated with.

Table 8.
Adjusted risk of INR variability and TTR 2.0-4.0 in relation to the outcomes.

	Hazard ratio (95% CI) per a change of 1 SD of the predicting variable			
	Combined endpoint	**Thromboembolism**	**Major bleeding**	**Death**
Log INR Variability	1.30 (1.11-1.52)	1.55 (1.03–2.34)	1.20 (0.93–1.57)	1.47 (1.11–1.93)
TTR 2.0-4.0	0.71 (0.61-0.83)	0.86 (0.62-1.20)	0.61 (0.49-0.77)	0.70 (0.58-0.83)

Major bleeding was adjusted for age, hypertension and eGFR. Death was ajdusted for age, hypertension, diabets, eGFR and time since valve replacement. The combined endpoint was adjusted for age, hypertension, diabetes, eGFR, heart failure and time since valve replacement.

The level of INR variability was assessed within in the three different levels of TTR to investigate these anticoagulation measures in the same model. The reference group was low variability within in the highest TTR group (hypothetical best group) in which the other five groups were compared to. This age-adjusted model presented in figure 13, demonstrates that for the combined endpoint, high variability was significantly increased in the high and low TTR compared to the high variability/ low TTR-group. A trend of increased risk for higher variability is observed for all endpoints.

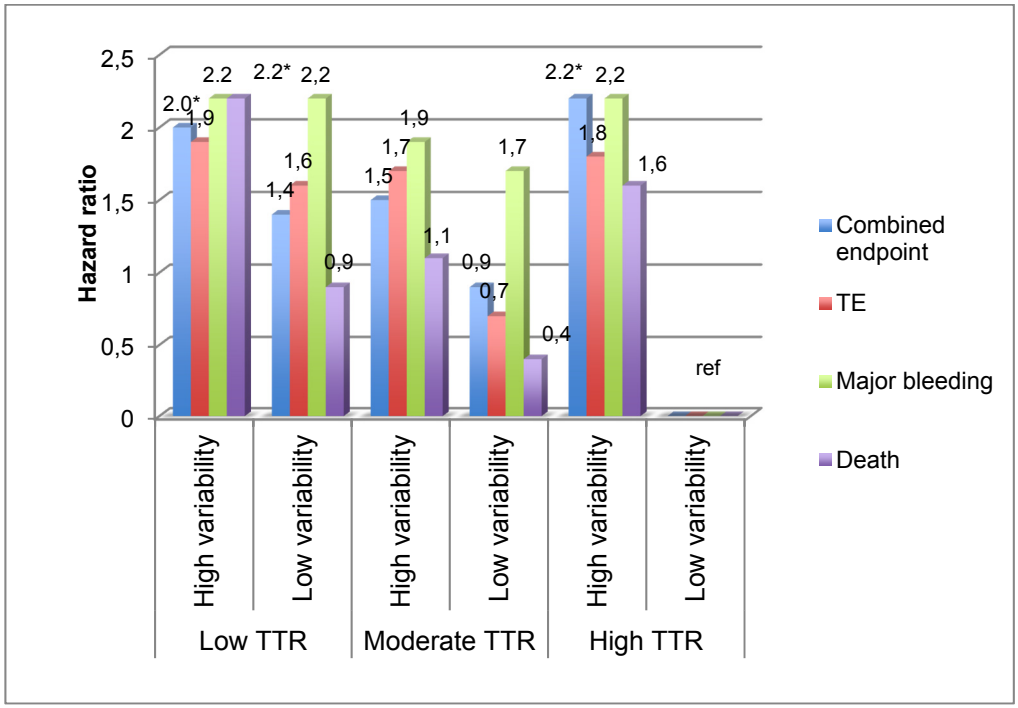


Figure 13.
Age-adjusted hazard ratios for high and low INR variability within different levels of TTR 2.0-4.0 compared to high TTR/low variability.
Age-adjusted HR; * p <0.05; TE, thromboembolism

Intensity of anticoagulation and adverse events

The time spent within designated INR ranges of 0.5 each was estimated for all patients during the period, and the incidence rates of TE and major bleeding events were calculated according to the INR values obtained at the time of the event. This allowed us to estimate the incidence rates within designated INR ranges. Incidence rates of TE and major bleeding for all patients with MHV is plotted with 95% CI in figure 14.

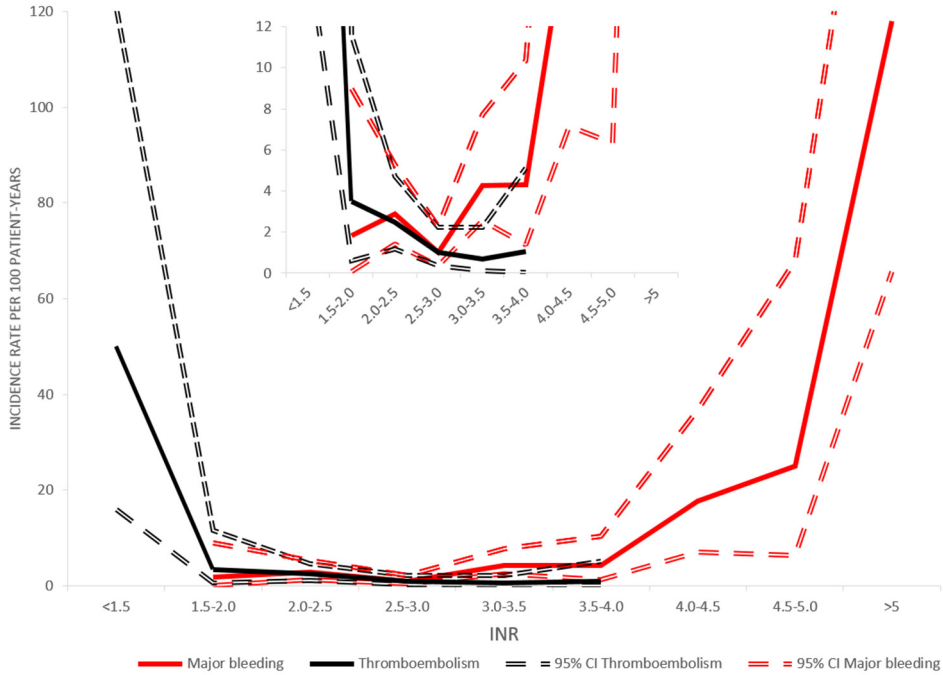


Figure 14.
Rate of incidence per 100 patient-years with 95% CI according to the INR at the time of event in relation to duration of treatment within designated INR ranges.
Upper image an enlargement with scaled incidence rate.

The major bleeding event rates are relatively balanced between 2-3 per 100 patient-years until INR 3.0, which then increases to approximately 4 per 100 patient-years to the level of INR 4.0. Subsequently, there is a sharp rise above INR >4.0 in the event rate. As for the TE-events, the event rate are low (≤1 per 100 patient-years) when INR >2.5 and rises considerably to 2.5 and 3.5 per 100 patient-years in the INR ranges of 2.0-2.5 and 1.5-2.0 respectively. When INR falls under 1.5 the incidence of TE rises sharply as plotted in figure 14.

Paper IV

The cohort consisted of 4,810 treatment periods with MHV and embraced 3,751 AVR, 866 MVR and 193 with combined AVR/MVR. These treatment periods consisted of 3,916 patients. Mean follow-up time was 4.5 years (IQR 1.5-6) and

yielded 18,362 patient-years of data. A total of 1,460 (30%) treatment periods were started (received a MHV) during the study period.

Target INR and TTR

In the study period there were a wide variations of INR target ranges, mostly due to individual assessments, prosthesis selection and position, and local traditions. For AVR, TTR 2.0-3.0 regardless of the actual INR target was 74.2% for 3,656 treatment periods (95 patients with insufficient INR values). Seventy-four % had an INR target of 2.0-3.0. The INR target of 2.5-3.5 and 2.0-4.0 was prescribed for 4.3% and 11.3% respectively.

The proportion of AF was 26% and 22.4% (p =0.35) for the INR targets of 2.0-3.0 and 2.5-3.5 respectively. Corresponding proportions of heart failure was 20.1% and 20.5% (p =0.92) respectively, and previous stroke 10.0% and 14.3% (p =0.11) respectively.

For 866 treatment periods with MVR, TTR for INR target range 2.0-3.0 was 67.2%, in which 52% of the patients had this INR target. The target range of 2.5-3.5 and 2.0-4.0 was prescribed for 21.5% and 15.2% respectively.

The incidence of stroke/TE and major bleeding events within the target range 2.0-3.0 vs. 2.5-3.5 and 2.0-4.0 are presented in table 9. There were no significant difference in stroke/TE and major bleeding between the target ranges in AVR and MVR.

Stroke/TE

A total of 244 stroke/TE occurred in the period. The rate of stroke/TE and major bleeding are presented in table 10. First and total rate of major bleeding is reported. The rate of TE in AVR shows a relatively flat increasing trend with increasing age. The rate of TE for patients with AVR between 60-70 years and 70-80 years was 1.0 and 1.7 per 100 patient-years, respectively (p =0.004). For patients with MVR, there was a similar flat curve for the rate of TE between 40-80 years of age. The event rate for 60-70 and 70-80 years was 1.5 per 100 patient-years for both age categories.

Major bleeding

A total of 587 major bleeding events occurred; 196 gastrointestinal, 92 intracranial and 299 other bleeding events. First and total event rates for major bleeding for the different valve positions are presented in table 10. The major bleeding events were plotted against age categories and showed a fairly balanced incidence rate between the ages of 40-70 years, which then increases substantially. The rate of major bleeding for patients with AVR between 60-70 years and 70-80 years was 2.2 and 2.9 per 100 patient-years, respectively (p =0.05). The incidence of major bleeding in MVR is considerably higher than AVR (3.9 vs. 2.6 per 100 patient-years; p <0.001) and shows a steep curve following 70 years of age. The rate of major bleeding for patients

with MVR between 60-70 years and 70-80 years was 2.6 and 4.1 per 100 patient-years, respectively (p =0.10).

Survival

The overall mortality during follow-up for AVR was 8.9% (281/3170), 11.9% (71/598) for MVR and 12.8%(19/148) for combined AVR/MVR. For patient that received their valve replacement during the study period, actuarial survival with AVR at 1, 3 and 5 years were 98.0%, 96.2% and 91.9% for 987 patients. Patients with isolated MVR had 93.3%, 91.5% and 85.8% respectively for 145 patients.

Risk factors for TE and major bleeding

Variables that have known association to TE and major bleeding were tested in a univariate and multivariate analysis to investigate the association to the outcomes, table 11. On univariate analysis for patients with AVR, inly age and previous stroke/TIA emerged as risk factors for stroke/TE, which also were significant in the multivariate analysis. AF and heart failure did not show any trends towards association in either analysis. For major bleeding, age and previous major bleeding emerged as independent risk factors, with kidney failure and alcohol overconsumption being borderline significant.

Propensity score matching for subgroups of cut points of 60 and 65 years of age

To reduce selection bias for the different thresholds of age, two different propensity score matched groups with AVR were conducted for patients over/under 60 years, and one over/under 65 years. Patients with isolated primary AVR (concomitant CABG excluded) during the study period provided a cohort of 920 patients. Tables 12 a-b present the baseline characteristics of the covariates before and after matching. There were no significant differences for any of the measured covariates of interest in the matched cohorts. The PSM-cohort of 60 and 65 years had a median follow-up time of 2.2 and 2.1 years, respectively and 1,551 and 1,108 patient-years of data respectively. The incidence rates and hazard ratios for the adverse events, mortality and the combined endpoint are presented in table 13. There was no significant difference between the events for the lower and higher age category. There was however a non-significant trend towards higher mortality rate for patients >60 years (n =13) compared to patients <60 years (n=6), HR: 2.2; p =0.11. There was no difference in the mortality rate the first postoperative year. Major bleeding events were numerical higher for the higher age categories, whereas the rate of stroke/TE was consistent between the groups. The combined endpoint was fairly balanced in PSM-cohort of 60 (4.8 and 5.6 per 100 patient-years, p =0.5) while in the group >65 years showed a numerical increasing trend towards higher rate of the combined endpoint (5.6% and 7.5 per 100 patient-years, p =0.28). Kaplan-Meier-estimated curves for the

combined endpoint in the PSM-cohorts are shown in figure 17 a-b. There were no significant differences for the combined endpoint at mid-term in neither cohort.

Table 9.
Rate of stroke/TE and major bleeding events in relation to target INR.

AVR	Stroke/TE	Rate	Major bleeding	Rate
2.0-3.0	139	1.29 (1.09-1.52)	257	2.44 (2.15-2.76)
2.5-3.5; 2.0-4.0	27	1.20 (0.79-1.75)*	67	3.07 (2.38-3.90) †
MVR				
2.0-3.0	26	1,73 (1.14-2.51)	61	4.02 (3.07-5.16)
2.5-3.5; 2.0-4.0	8	1.77 (1.03-2.83)*	29	2.98 (1.99-4.28) ‡

Rate is incidence per 100 patient-years (95% CI); AVR, aortic valve replacement; MVR, mitral valve replacement; * not significant; † P =0.10; ‡ P =0.18.

Table 10.
Rates of stroke/TE and major bleeding events.

	All patients n= 4,810	AVR n= 3,751	MVR n= 1,051
Stroke/TE	1.36 (1.20-1.54)	1.31 (1.13-1.50)	1.62 (1.20-2.14)
First major bleeding	2.91 (2.66-3.17)	2.64 (2.38-2.92)	3.93 (3.24-3.72) †
Intracranial	0.50 (0.41-0.62)	0.41 (0.32-0.53)	1.0 (0.68-1.41) †
Gastrointestinal	1.09 (0.94-1.25)	0.99 (0.84-1.16)	1.49 (1.09-1.99) ‡
Other	1.68 (1.50-1.88)	1.56 (1.36-1.77)	2.11 (1.62-2.70) ‡
Total major bleeding	3.20 (2.95-3.46)	2.89 (2.63-3.17)	4.49 (3.77-5.31) †

Rate is incidence per 100 patient-years (95% CI); AVR, aortic valve replacement; MVR, mitral valve replacement; † P <0.001; ‡ P <0.05. Total major bleeding covers all subtypes of the major bleeding events, with only one event of each subtype permitted.

Table 11.
Risk factors of stroke/TE and major bleeding in patients with AVR.

Stroke/TE	Univariate	P-value	Multivariate	P-value
Age	1.03 (1.01-1.04)	<0.001	1.02 (1.004-1.04)	0.012
Female	1.22 (0.88-1.69)	NS	1.03 (0.74-1.44)	NS
Kidney failure	0.88 (0.28-2.78)	NS	0.81 (0.25-2.56)	NS
Previous stroke	2.89 (1.95-4.00)	<0.001	2.44 (1.69-3.54)	<0.001
Diabetes	0.98 (0.57-1.66)	NS	0.83 (0.48-1.44)	NS
Hypertension	0.76 (0.54-1.06)	NS	1.18 (0.83-1.67)	NS
Atrial fibrillation	1.16 (0.82-1.64)	NS	1.0 (0.69-1.44)	NS
Heart failure	1.04 (0.71-1.52)	NS	0.90 (0.60-1.35)	NS
Vascular disease	1.79 (1.05-3.05)	0.03	1.64 (0.95-2.84)	0.075
Major bleeding				
Age	1.02 (1.02-1.03)	<0.001	1.02 (1.01-1.03)	<0.001
Female	1.27 (1.02-1.60)	0.035	1.14 (0.90-1.43)	NS
Hypertension	1.20 (0.95-1.52)	NS	1.03 (0.81-1.32)	NS
Kidney failure	2.23 (1.30-3.80)	0.003	1.71 (0.98-2.97)	0.057
Previous stroke	1.10 (0.79-1.55)	NS	0.89 (0.64-1.26)	NS
Liver failure	1.30 (0.32-5.20)	NS	1.35 (0.33-5.49)	NS
Alcohol overconsumption	2.05 (1.09-3.84)	0.025	1.81 (0.96-3.41)	0.069
Previous bleeding	2.85 (2.22-3.67)	<0.001	2.49 (1.91-3.25)	<0.001

HR, hazard ratio; CI, confidence interval; other abbreviations as table 1. Multivariate analysis adjusted for the variables listed for each event and time since start of study period.

Table 12a.
Propensity score matched cohort by age of 60 years.

	Cohort		PSM		
	n=547	n=373	n=307	n=307	
	<60 yr	>60 yr	<60 yr	>60 yr	SMD
Age (median, IQR)	52.4 (44-57)	64.7 (62-68)	54.5 (47-58)	64.7 (62-68)	
Female	135 (21.8)	130 (29.5)	82 (26.7)	75 (24.4)	0.05
Kidney failure	10 (1.6)	19 (4.3)	5 (1.6)	8 (2.6)	0.06
COPD	16 (2.6)	23 (5.2)	12 (3.9)	11 (3.6)	0.02
Liver dysfunction	6 (1.0)	5 (1.1)	2 (0.7)	4 (1.3)	0.06
Previous stroke	38 (6.1)	52 (11.8)	23 (7.5)	23 (7.5)	0
Diabetes	44 (7.1)	65 (14.8)	34 (11.1)	41 (13.4)	0.06
Hypertension	192 (31.1)	189 (43.0)	124 (40.4)	126 (41.0)	0.01
Antiplatelet agent	145 (23.5)	138 (31.4)	100 (32.6)	96 (31.3)	0.03
Aspirin	144 (23.3)	130 (29.5)	99 (32.2)	95 (30.9)	0.03
NSAID	49 (7.9)	31 (7.0)	23 (7.5)	24 (7.8)	0.01
SSRI	45 (7.3)	35 (8.0)	21 (6.8)	23 (7.5)	0.03
Estrogen	9 (1.5)	19 (4.3)	7 (2.3)	6 (2.0)	0.02
Atrial fibrillation	135 (21.8)	194 (44.1)	94 (30.6)	106 (34.5)	0.08
Endocarditis	84 (13.6)	29 (6.6)	19 (6.2)	19 (6.2)	0.000
Rheumatic heart disease	17 (2.8)	21 (4.8)	6 (2.0)	6 (2.0)	0
Previous GI-bleeding	13 (2.1)	20 (4.5)	6 (2.0)	9 (2.9)	0.06
Dyslipidemia	14 (2.3)	26 (5.9)	11 (3.6)	17 (5.5)	0.09
Heart failure	109 (17.6)	116 (26.4)	60 (19.5)	63 (20.5)	0.02
PAH	8 (1.3)	8 (1.8)	0	0	NA
Vascular disease	28 (4.5)	24 (5.5)	14 (4.6)	15 (4.9)	0.01
Previous ICH	7 (1.1)	7 (1.6)	4 (1.3)	5 (1.6)	0.02
Other previous bleeding	17 (2.8)	17 (3.9)	5 (1.6)	9 (2.9)	0.07
Alcohol	17 (2.8)	2 (0.5)	2 (0.7)	2 (0.7)	0
Previous PCI	7 (1.1)	14 (3.2)	7 (2.3)	7 (2.3)	0
Anemia	27 (4.4)	45 (10.2)	12 (3.9)	15 (4.9)	0.03

PSM, propensity score matched group; COPD, chronic obstructive pulmonary disease; NSAID, non steoridal anti-inflammatory drugs; PAH, pulmonary arterial hypertension; PCI, percutaneous coronary intervention; SMD, standardized mean difference between the groups in the propensity matched cohort

Table 12b.
Propensity score matched cohort by age of 65 years.

	Cohort		PSM		
	n=738	**n=182**	**n=293**	**n=156**	
	<65	**>65**	**<65**	**>65**	**SMD**
Age (median, IQR)	56.2 (48.2-60.1)	68.5 (66.4-73.2)	58.2 (49.6-61.4)	68.4 (66.4-71.8)	
Female	156 (21.1)	60 (33.0)	71 (24.2)	41 (26.3)	0.04
Kidney failure	14 (1.9)	6 (3.3)	9 (3.1)	4 (2.6)	0.05
COPD	25 (3.4)	8 (4.4)	12 (4.1)	7 /4.5)	0.03
Liver dysfunction	5 (0.7)	3 (1.6)	2 (0.7)	1 (0.6)	0.03
Previous stroke	47 (6.4)	26 (14.3)	28 (9.6)	15 (9.6)	0.03
Diabetes	63 (8.5)	35 (19.2)	34 (11.6)	19 (12.2)	<0.01
Hypertension	260 (35.2)	91 (50.0)	130 (44.4)	68 (43.6)	0.06
Antiplatelet agent	197 (26.7)	57 (31.3)	79 (29.0)	48 (30.8)	0.06
Aspirin	190 (25.7)	55 (30.2)	76 (25.9)	48 (30.8)	0.08
NSAID	65 (8.8)	8 (4.4)	22 (7.5)	8 (5.1)	0.11
SSRI	51 (6.9)	11 (6.0)	24 (8.2)	9 (5.8)	0.11
Estrogen	14 (1.9)	9 (4.9)	8 (2.7)	5 (3.2)	0.03
Atrial fibrillation	182 (24.7)	89 (48.9)	119 (40.6)	68 (43.6)	0.06
Endocarditis	77 (10.4)	9 (4.9)	26 (8.9)	9 (5.8)	0.15
Rheumatic heart disease	13 (1.8)	8 (4.4)	9 (3.1)	3 (1.9)	0.08
Previous GI-bleeding	15 (2.0)	6 (3.3)	7 (2.4)	4 (2.6)	<0.01
Dyslipidemia	24 (3.3)	11 (6.0)	16 (5.5)	10 (6.4)	<0.01
Heart failure	122 (16.5)	58 (31.9)	80 (27.3)	38 (24.4)	0.12
PAH	5 (0.7)	0			
Vascular disease	38 (5.1)	10 (5.5)	14 (4.8)	6 (3.8)	0.04
Previous ICH	12 (1.6)	2 (1.1)	5 (1.7)	1 (0.6)	0.09
Other previous bleeding	17 (2.3)	10 (5.5)	9 (3.1)	5 (3.2)	<0.01
Alcohol overconsumption	12 (1.6)	2 (1.1)	5 (1.7)	2 (1.3)	0.06
Previous PCI	13 (1.8)	6 (3.3)	7 (2.4)	4 (2.6)	0.02
Anemia	37 (5.0)	17 (9.3)	17 (5.8)	11 (7.1)	0.03

Abbreviations as table 11a.

Table 13.
Annular event rates and hazard ratios in the propensity score matched groups between the age categories.

	<60 yr*	>60 yr*	HR	95% CI	p-value
Stroke/TE	1.59	1.32	0.84	0.36-1.93	0.66
Major bleeding	2.54	3.18	1.23	0.67-2.26	0.51
Mortality	0.77	1.69	2.19	0.83-5.77	0.11
Combined endpoint	4.84	5.61	1.15	0.73-1.82	0.54
	<65 yr	**>65 yr**			
Stroke/TE	1.93	1.98	1.007	0.41-2.50	0.99
Major bleeding	3.06	3.96	1.28	0.64-2.53	0.49
Mortality	1.34	1.66	1.22	0.44-3.36	0.70
Combined endpoint	5.58	7.50	1.32	0.79-2.20	0.28

HR, hazard ratio

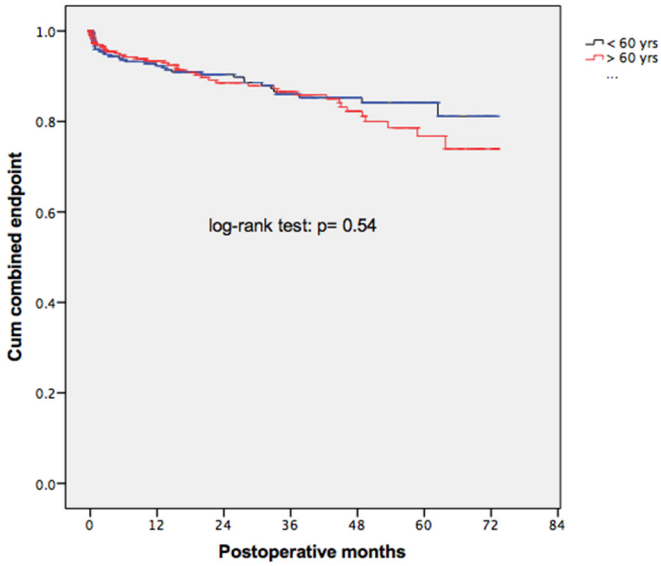


Figure 17a.
Kaplan-Meier curve comparing the combined endpoint in propensity score matched patients aged <60 years and >60 years who had undergone aortic valve replacements with mechanical prosthesis.

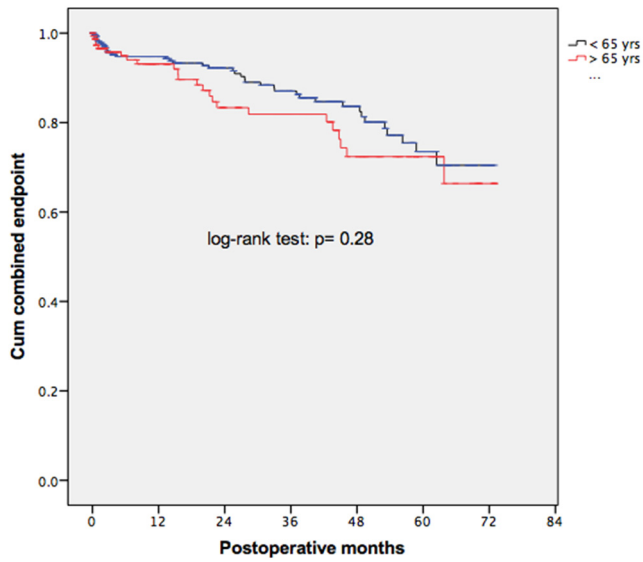


Figure 17b.
Kaplan-Meier curve comparing the combined endpoint in propensity score matched patients aged <65 years and >65 years who had undergone aortic valve replacements with mechanical prosthesis.

Discussion

Incidence of adverse events

The incidence of TE and major bleeding were assessed in the cohort of Malmö/Sundsvall, and in the nationwide population in Auricula. The incidence of these events were prospectively registered, and retrospectively thoroughly validated in the medical records in paper I-III. This method was at more thorough compared to paper IV and probably reflected a more accurate incidence although with considerably fewer patients, since paper IV used the NPR for the extraction of diagnose codes. The reported incidences of TE from randomized trials with bileaflet aortic valves have ranged from 0.4 to 2.6 per 100 patient-years, all depending on INR target ranges and different patient characteristics that were included in the trials (29-31, 47, 112). Recent trials in particular have enrolled relatively healthy patients with a low number of events occurring, which have undermined the statistical power and reliability of the trials. One of the major strengths with our study is the fact that, as long as warfarin therapy was still maintained no patients were excluded, and could have resulted in a more accurate representation of the adverse events in clinical practice. Additionally, it seems that the variability of TE and major bleeding events from one study to another with similar prosthesis, are more dependent of the patient-related risk factors, INR targets and treatment quality than the prosthesis selection itself.

We reported a TE incidence of 1.8 and 2.2 per 100 patient-years for AVR and MVR respectively in paper I, and significantly higher than LOWERING-IT trial (31) and ESCAT trial (30), which compared low intensity INR target to standard INR target range. The most noteworthy difference compared to our study was that the LOWERING-IT trial enrolled low risk patients with a mean age of 50, whereas the ESCAT trial had a mean age of 60 with a slightly more burdened risk factor profile than LOWERING-IT trial. Our cohort in paper I, had a mean age of 68 years and a considerable higher proportions patients with heart failure, AF, hypertension and diabetes. These are established risk factors and likely to contribute to the increased incidence of TE. The PROACT trial also compared low intensity INR target (1.5-2.0) to standard INR target (2.0-3.0) in patients with the aortic On-X valve (47). The incidence of TE was 1.6 and 2.7 per 100 patient-years respectively with no statistical significance. The higher observed incidences compared to the previous randomized

trials is partly due to the inclusion of high risk patients with chronic AF, left ventricular dysfunction and allowed concomitant CABG, valve repair, maze procedure, which better reflects our patient population than the previously mentioned trials.

The results in paper IV reflect a comprehensive view of the incidences of TE and major bleeding in total in Sweden. The sample size and number of events are major strengths that the randomized trials are lacking. The incidence rates are also plotted against age categories to illustrate the importance of age as a risk factor in TE and major bleeding, which can be of importance since prosthesis selection in patients 50-70 years is highly debated. The rates of stroke in AVR seem to increase linearly with age, however with a relatively stable incidence until 70 years of age where it steeps slightly. A similar trend is seen in MVR and combined prosthesis where the curve steepens a bit after 80 years of age.

In contrast, major bleeding rates have a more steepened linear association with age in both valve groups across age categories. The significant difference in bleeding rates between AVR and MVR probably reflects the different INR target ranges and is not related to the position of prosthesis. This was also confirmed by Horstkotte et al(113) and the more recent studies comparing low INR target range with standard target ranges (31, 47). The major bleeding events were doubled compared to TE events in the AVR group, and nearly 2.5-folded in the MVR group, with contemporary INR target ranges. Historically, bleeding rates have outweighed TE-events numerically across many studies, in particular older studies that used wide and high INR target ranges. In view of these incidence rates, raising INR target ranges in presence of patient-related risk factors would probably increase the risk of bleeding further, with no evidence of decreasing the risk of TE. Another aspect of the incidence rates across the age categories, is the contribution of data that can support the ongoing debate whether patients between 50-70 years of age should receive a bioprosthesis or MHV.

Recently, small series of cases have shown that loss of high molecular weight multimers of VWF due to high fluid shear conditions in patients with prosthetic paravalvular leak or stenosis (52, 53, 114). The acquired abnormal VWF multimers were even associated with increased bleeding risk in the study of Blackshear et al (52). Given the high gastrointestinal bleeding incidence in paper I and IV, it raises the question whether AVWS is a major contributing factor of the increased bleeding risk. Unfortunately, echocardiographic data were not available for the cohort to assess if there was an association between prosthesis dysfunction and bleeding risk.

INR target

Because of the different INR target ranges used in the cohorts in Malmö and Sundsvall, propensity score matching was utilized to obtain a matched cohort for

comparison. The matched cohort demonstrated a numerical higher rate of TE and a doubled increase in major bleeding events for the cohort in Malmö (INR 2.0-4-0), although data were not significant. Despite similar achieved mean INR in the cohorts, the trend, in particular for major bleeding, there was a clear trend for increased major bleeding events with no evident lower incidence of TE with the higher INR target range in Malmö. Furthermore, the widened target range is associated to higher INR variability, which in paper III is independently associated to adverse events, which could explain the increased risk of events seen.

The INR-specific incidence rates in paper III shows that major bleeding events increases from approximately 1.8-2.9 per 100 patient-years for INRs in the range 1.5-3.0, to 4.3 per 100 patient-years for INRs in the range 3.0-4.0, and rises sharply to >17 per 100 patient-years when INRs are >4.0. Although confidence intervals are wide within the designated INR intervals, a clear trend is observed suggesting that the optimal INR range for bleeding risk is below 3.0 and definitely below 4.0. The rate of TE was highest at 50 events per 100 treatment-years when INRs are <1.5, and 3.5 and 2.5 per 100 treatment-years for INRs in the range 1.5-2.0 and 2.0-2.5 respectively. Above the INR of 2.5 event rates, were balanced and did not go below approximately 1.0 per 100 treatment-years. The most optimal anticoagulation intensity should be defined as the level at which the incidence of both TE and major bleeding is lowest. These measures imply that the optimal intensity of anticoagulation treatment could be when INRs are in the range of 2.5-3.0, where the incidence of major bleeding and TE are lowest. Combining the rate of major bleeding and TE, the incidence is 1.0 per 100 treatment-years for INR 2.5-3.0, whereas the rate is approximately 2.7 for INR 1.5-2.5 and INR 3.0-4.0.

The recommendations for the appropriate anticoagulation therapy for patients with MHV have over time ranged from 2.0-4.5 with various prosthesis and under different circumstances. In 1995, Cannegieter et al.(92) published a paper investigating the optimal intensity of anticoagulation treatment in patients with early models of MHV, mostly tilting disc valves. Since prothrombin time was standardized internationally in 1985, earlier studies could not be included in this analysis. During this period a prothrombin time of 3.6-4.8 was used as target range. The authors stated that the most optimal range was 2.5-4.9, at which an incidence of all adverse events of 2.0 per 100 patient-years occurred. Below and above this range, the incidence of TE and bleeding respectively rose sharply. With better-designed valves that were less thrombogenic (bileaflet valves), less aggressive anticoagulation treatment was required. Despite lack of firm evidence, guidelines lowered INR values from 3.0-4.5 to 2.0-3.5 depending on valve position.

A meta-analysis from 2003 (41) included 35 studies, mostly from the 90's, which compared higher INR target ranges to lower levels. A cutoff point at INR 3.0 was chosen for high and low values, and showed that the higher INR target ranges were

associated with a significantly decreased risk of TE (RR: 0.73), but increased significant risk of major bleeding (RR: 1.23) in patients with AVR. The risk of TE and major bleeding combined was significantly lower (RR: 0.94) for the high INR target range. Similar results were found for patients with mitral MHV. Consequently, the authors stated that patients with MHV would benefit from high-intensity warfarin therapy. There are several issues that should be pointed out before extrapolating these results to contemporary treatment. Firstly, some studies used older models of valve prosthesis that are not implanted anymore and are associated with a higher risk of TE. Secondly and most importantly, the anticoagulation treatment in terms of quality was likely inferior than anticoagulation treatment today. The randomized trials during the period of the included trials yielded a time spent in the therapeutic range of approximately 50-70% and within wide target ranges(55, 115) where it is unlikely that these observational cohorts achieved better control in the anticoagulation treatment compared to the treatment today. The INR variability was likely at that time increased based on the wide INR ranges that were used, which is associated with adverse events and death in paper III. Thirdly, the defined high and low intensity groups were in many cases overlapping due to wide INR ranges used and the achieved (vs. intention to treat INR target) INR results were not considered in the analysis.

The optimal anticoagulation intensity for patients with MHV was once again investigated in the study by Torn et al (116), which included patients between 1994-1998 with an INR target range of 3.6-4.8. The INR level that provided the lowest overall incidence of TE and major bleeding was at INR 2.5-3.0 (2.0 per 100 patient-years), confirming the data from our cohort. Event rates were only slightly higher for INR 3.0-4.4, and rose considerably when INRs were <2.0 (27 per 100 treatment-years). When weighing events as fatal or life threatening, the level of the intensity range did not change. Event rates were however very low within each intensity range and with wide confidence intervals. Of special note, is the substantial increase in TE/ischemic stroke when INR falls below 2.5 in these studies (92, 116), and that the rate of major bleeding starts to rise once INR >5.0. These results are in conflict with our results, and could be attributable to the valve prosthesis used (nearly 80% tilting disc and caged ball) that are associated with increased risk of TE when INR levels are below 2.5. The increased bleeding rates with INR >3.0 in our cohort can in particular be attributed the higher mean age of 70 years compared to the other cohorts, in which 83% and 68% respectively were <69 years. In a subgroup analysis by Cannegieter et al patients >70 years had a steeped curve of major bleeding upwards when INR >4.0. In addition the risk of major bleeding in warfarin-treated patients is highly associated with increasing age(117). The tight INR control in terms of high TTR could be more sensitive for bleeding events when INR values exceeds 4.0, since TTR 2.0-4.0 is an independent risk factor of major bleeding as presented in paper III.

Chronic kidney disease

The effect of impaired renal function assessed by eGFR on adverse events and mortality was investigated in paper II. The rates of major bleeding, death and the combined endpoint increased as the eGFR decreased. Each increase of unit in eGFR (ml/min/1.73 m^2) independently decreased the risk of major bleeding by 2%, death by 3% and the combined endpoint by 1% while there was no association with TE. The adjusted risk for the combined endpoint for eGFR <30 ml/min/1.73 m^2 compared to the >60 ml/min/1.73 m^2 was more than three times higher. Additionally, the proportion of patients with deranged INR values in terms of proportion of INR values >4.0 and INR >3.0 with decreasing TTR 2.0-3.0 was higher for each decreasing eGFR stratum.

To the best of our knowledge, paper II is the first report demonstrating the association between impaired renal function estimated as eGFR and adverse events in patients with MHV. This association was independent of clinical and demographic risk factors, which is remarkable since increasing age, hypertension, diabetes and heart failure are common and often the etiology of CKD. This could be due to the fact that the severity, duration and treatment status of abovementioned risk factors are not accounted for in the analysis, whereas CKD is a marker for end-organ damage and much stronger predictor of adverse events.

Since other studies with eGFR across different CKD stages are absent in patients with MHV, comparisons cannot be made. Remarkably, no correlation between eGFR as a continuous variable or across strata, and TE could be found. The effect of impaired renal function has been investigated in patients with AF on oral anticoagulation treatment in observational prospective and retrospective cohorts(118-121). A recent meta-analysis (122) showed that in patients with non-end-stage CKD (no dialysis or transplantation), warfarin reduced the risks of ischemic stroke/TE by 30%, with no significant change in the risk of major bleeding compared to patients not taking warfarin. Warfarin had however no effect on the risks of stroke/TE in patients with end-stage CKD, and was associated with a significant increased risk of 30% in major bleeding events.

Sweden has generally high level of anticoagulation control, as reflected by high TTR compared to other countries and even controlled randomized trials (123). Thus the Swedish study of Carrero et al that investigated patients with AF at different levels of eGFR following acute myocardial infarction is interesting, since it did not show any difference in the incidence of ischemic stroke across CKD stages, as in our study. In contrast, the randomized AMADUES trial(120) demonstrated an increased risk of stroke/TE with worsening renal function in anticoagulated patients. These results could be attributable to the quality of anticoagulation treatment in terms of high TTR in our cohort and probably in the study of Carrero et al. This is also consistent with another Swedish study (118), which indicated that patients with AF and renal

impairment with TTR >70% had fewer strokes and particularly fewer major bleeding events than patients with lower TTR. The large Danish cohort study by olesen et al(121) showed that among non-end-stage CKD, the risk of stroke/TE was not influenced by the severity of the renal disease. This study however assessed the renal function by the intensity of treatment with loop diuretics. It seems that the predictive effect of low eGFR on the risk of TE may be leveled out when INR control is tight (high TTR) to a certain level of renal function in patients with AF. This association was found in our cohort as well, despite that thrombus formation in patients with MHV probably have other mechanisms than in AF. The argument of appropriate anticoagulation treatment in terms of high TTR and the diminished association between eGFR and TE risk could also be applied to patients with MHV who also have AF. There was no trend toward association between AF and stroke/TE in our cohort of patients with MHV, in which guidelines recommend higher INR target due to increased risk of TE. High TTR (> 70%) might be sufficient to eliminate the impact of AF on the risk of TE.

The increased risk of bleeding in our cohort with worsening renal function may also be attributable to poorer anticoagulation control, where decreasing TTR and proportions of INR above 3.0 and 4.0 were more common with each decreasing eGFR stratum. This is consistent with another Swedish AF study(124) in a setting with high TTR where supratherapeutic INR values were correlated with bleeding events, and with the study by Limdi et al (125).

There is a strong correlation between decreasing eGFR and increased risk of bleeding in patients with AF on oral anticoagulation treatment(118, 120, 124). CKD is also a major predictor of cardiovascular events and death for patients without anticoagulation treatment(100). Paradoxically, due to disturbances in the coagulation cascade, fibrinolytic system, platelets, endothelium and vessel wall, patients with CKD have increased risk of both bleeding and TE-events (126, 127). An explanation could be that patients with CKD suffer from varying degree of inflammation, which also influences hemostasis. Furthermore, microparticles that are formed from plasma membranes are increased in patients with CKD and cancer, and have recently been discovered to have potent procoagulatory effect (127).

There are no publications regarding non-end-stage CKD in patients with MHV, but some retrospective studies of patients with end-stage CKD undergoing valve replacement surgery have been published. The large retrospective cohort by Herzog et al (102) compared the long-term survival between bioprosthesis and MHV in patients with dialysis in the United States between 1978-1998. There was no significant difference in survival between the groups and the authors stated that existing guidelines, that recommended bioprosthesis in these patients should be rescinded. The European guidelines recommend favoring bioprosthesis over MHV due to the warfarin-related complications, despite the accelerated structural valve deterioration in

patients with bioprosthesis and end-stage CKD. The observational character of this and other smaller studies(103, 104), may be associated with selection bias, and the study of Herzog et al refers to patients with shorter life expectancy than dialysis patients today(128), specially outside of the United States. Since life expectancy in dialysis patients is much longer today, the risk of early calcification of a bioprosthesis should be taken into account when selecting valve prosthesis. However, a major disadvantage of MHV is the need of VKA treatment, which in end-stage CKD increases the risk of major bleeding substantially (121). There is association of increased vascular calcification in patients receiving warfarin, especially in patients with CKD, due to the inhibition of matrix gla protein by warfarin that normally inhibits the process of medial calcification (129).

A major gap in evidence that remains is prosthesis selection in patients with eGFR 15-60 ml/min/1.73 m^2. As for our cohort, there is an increasing risk of major bleeding and death as the eGFR decreases, without an association with stroke/TE. If we hypothesize that all patients with bioprosthesis do not have an indication for VKA treatment, the results of Carrero et al can give some guidance for bleeding events across CKD stages. The major bleeding events increased in patients with AF without VKA treatment with lower CKD stage, and were not significantly lower than the VKA-treated patients. Similar results were found in a meta-analysis where warfarin did not alter the risks of major bleeding in patients with non-end-stage CKD(122).

Due to lack of evidence in this area, individualized assessment of each patient must be made, and if life expectancy is considered to be longer than the presumed durability of the bioprosthesis, the complication rates in our cohort and the studies mentioned above must be considered. It is important to emphasize that many patients with CKD that are considered for valve replacement surgery could have other indications of VKA treatment (most commonly AF), and that the abovementioned studies concerns patients with AF and not valve prosthesis. Consequently, extrapolation to the selection of MHV or bioprosthesis is complicated. Naturally, the most correct way of addressing this issue would be a prospective randomized trial.

INR variability

The most accepted surrogate marker for the quality of anticoagulation treatment is TTR. The INR variability measures the stability and variance of anticoagulation and not the intensity as TTR does. Our results show that the log INR variability expressed per one SD has an equal predictive ability as TTR 2.0-4.0 for the combined endpoint of TE, major bleeding and mortality, and performs even better for mortality. Furthermore, our results suggest that reducing the risk of adverse events and the combined endpoint by achieving higher levels of TTR may be contingent on achieving low INR variability. There was a clear trend of increased risk of higher

variability in each level of TTR for the combined endpoint, with significant hazards in the high and low TTR level.

As for the TE-events, log INR variability significantly increased the risk by 55% with each unit increase in the SD, whereas TTR 2.0-4.0 was not associated with TE. An analysis demonstrates that the majority of TE-events (73%) occur during therapeutic INR range (2.0-4.0), and that the remaining percentage occur when INRs are below 2.0. The variability over time within or adjacent to therapeutic range seems to be more procoagulant than being associated with increased risk of bleeding in patients with MHV. The log INR variability was associated with a non-significant increased risk of major bleeding (HR: 1.20; CI 0.93-1.57), where as an increase in each unit of SD for TTR 2.0-4.0, decreased the adjusted risk significantly by 39%. Contrary to TE-events, 40% of the INR values at admission in patients with major bleeding events were above 4.0. It must be emphasized that the INR at admission is a minor contributing factor for the calculation of INR variability over time. The INR value at admission can however give a hint of the present circumstances circumstance, which is more applicable in assessing the INR specific incidence rates. Although the INR target range of 2.0-4.0 was used in our cohort, additional calculation using TTR 2.0-3.0 was made for all endpoints, which did not result in any significant associations to neither endpoint. This could be explained by the fact that this target range was not used and accordingly, sufficient number of INR values were outside 2.0-3.0, which may have diluted any correlation to the endpoints.

There are only few studies addressing the relationship and effect of these two anticoagulation measures. Razouki et al (95) showed in a retrospective cohort study among patients with AF that both log INR variability and TTR separately were associated with ischemic stroke and major bleeding. The adjusted model showed that low TTR compared to high TTR was more associated with both endpoints than high variability compared to low variability. Further, the INR variability was assessed in three TTR percentage intervals of 2.0-3.0 that constituted of <50%, 50-70% and >70%, which were lower levels than in our cohort used with TTR 2.0-4.0. Another drawback was that the study used automated data, which were not validated by chart review, as opposed to our study. The non-significant results for INR variability for major bleeding in our study, which were significant in the study of Razouki et al. could be due to few events and small sample size.

van Leeuween et al (96) showed in a case-control study in patients with MHV that high INR variability, three months prior to an event was associated with an increased risk of thrombotic events, but not major bleeding events. Combining the events, unadjusted risk was significantly associated with INR variability. No correlation could be found when INR measurement was extended to 6 or 12 months. A criticism regarding a time window of 3 months could be that to few INR measurements are liable for the calculation of INR variability, which could be uncertain and associated

with bias. Furthermore, the INR variability was dichotomized for all analysis, which causes considerable loss of power and residual confounding.

We selected a cutoff point of INR variability where the incidence of the combined endpoint was significant compared to the lowest variability group. This cutoff point was used to dichotomize the variable for some of the analysis. However, there is no validated threshold to distinguish between high and low INR variability to be adopted in the clinical practice. Clearly more data and studies are required for patients with MHV to determine a validated cutoff point for INR variability. A limitation of INR variability for adoption in clinical practice is that it is difficult to calculate manually, as is for TTR. Our suggestion would be to computerize the assessment of INR variability in the anticoagulation clinics, in addition to TTR, to obtain a broader perspective of the quality of anticoagulation given. It is clear that based on our and previous studies, INR variability adds an additional dimension, which further classify anticoagulation care on a much more detailed level. There is support that more frequent INR measurements in patients with self-monitoring and MHV reduce the INR variability(130). Patients with CKD and MHV, who present with inferior INR control (paper II), and have a higher risk of major bleeding events and death, could be potential candidates for self-monitoring or more frequent INR measurements compared to patients with normal renal function. Clearly, prospective studies are required to investigate if reducing INR variability by this method will reduce these adverse events.

Patient-related risk factors

The European and American guidelines currently recommend revising INR target intervals upwards to 2.5-3.5 for patients with aortic MHV, if risk factors such as AF, previous TE, left ventricle dysfunction, hypercoagulable condition, or an older generation mechanical prosthesis are present. The American College of Chest Physicians (ACCP) guideline states that the presence of these patient-related risk factors have been suggested to increase the risk of TE-events. However, the recommendation of revising INR upwards is cautious and not definite in these guidelines. The American Heart Association/American College of Cardiology (AHA/ACC) guidelines however, recommend revising INR with a class 1B recommendation. These recommendations are also shared by the European Society of Cardiology (ESC) guidelines, although without class recommendations. The discrepancy between guidelines clearly demonstrates the uncertainty regarding revision of anticoagulation treatment in presence of these risk factors.

In paper I, using univariate analysis, no association were found for age, mitral position, heart failure, AF or even previous stroke with TE-events. Only vascular disease emerged as an independent risk factor for TE. In Paper IV, only age, previous

stroke and vascular disease were significant using univariate analysis. Again, no trend toward an association between AF or heart failure, and TE-events were found. Age and previous stroke emerged as independent risk factors in the multivariate analysis. One could argue that in paper I, most patients had an INR target of 2.0-4.0, which could theoretically dilute any associations with AF and heart failure since the INR target interval is higher than recommended. However, this was not the case for the large cohort of patients in paper IV where 74% of the patients had an INR target interval of 2.0-3.0. Moreover, the proportions of AF, heart failure and previous stroke were similar in the different INR target ranges, which imply that clinicians in Sweden are reluctant to revise INR targets in presence of these risk factors.

Lower thrombogenicity of currently used MHVs have resulted in a decreased risk of TE-events compared to older generation valves. Although all TE-events in patients with MHV are defined as "prosthetic valve related morbidity", it does not reflect the etiology of such events, and it is not possible to distinguish if the thrombus formation is derived from the prosthesis or other underlying cardiac and vascular related comorbidities. Guideline recommendations are actually based on one review article by Horstkotte et al (35) from 1995, based on published papers from 1970-80s that summarize the understanding of thrombus formation in patients with MHV. This article concludes that with lower thrombogenicity prosthesis, factors such as AF, chamber dilatation and reduced left ventricular function may become more important contributors to TE than the prosthesis itself. Taking this into account, the authors stated that the intensity of anticoagulation should be considered based on risk score scheme based on their own experience. While the conception of etiology and increased risk of abovementioned risk factors may be true, there is no current evidence that revising INR upwards will decrease the risk of TE-events. Furthermore, older generation MHV with outdated intensity of anticoagulation were used during this period, and most importantly the quality of anticoagulation treatment was not considered in this review article or in the guidelines, when addressing the patient-related risk factors. Accordingly, there is a need for contemporary studies with tight INR control to identify firstly, if these risk factors are independently associated with an increased risk of TE, and secondly if revising INR target intervals upwards will actually decrease the risk.

Since the quality of anticoagulation treatment determines the risk of adverse events and death in patients with MHV(55, 131), failing to prove an association with AF or heart failure with TE must be interpreted in the view of the strict anticoagulation control. Thus, we have presented results within a small cohort of two centers with careful follow-up (paper I) and a large nation-wide cohort in Sweden (paper IV), that in patients with MHV with acceptable anticoagulation control, the risk of TE is not increased in presence of AF and heart failure. Consequently, these data challenge current guidelines recommending revising INR target ranges in patients with aortic MHV and presence of these risk factors. In addition, several studies have showed that

the risk of bleeding outweighs the risk of TE within standard INR target ranges, while it is more balanced in the lower target ranges. In paper IV, the doubled risk of major bleeding compared to TE/stroke confirms these findings. Aiming towards higher INR targets will most likely increase the bleeding further without a certain decrease in the risk of TE.

Risk factors of major bleeding in patients with MHV seem to be the same risk factors for other indication for anticoagulation treatment. In paper I, previous bleeding emerged as an independent risk factor, while age >75 years and alcohol overconsumption were borderline significant. In paper IV, independent risk factors were age, previous bleeding with borderline significance for renal failure and alcohol overconsumption. There are numerous studies investigating risk factors in warfarin-treated patients with AF(132, 133) that confirms the risk factors in our studies. Since anticoagulation treatment cannot be withdrawn in patients with MHV, score schemes such as HAS-BLED score can be used to take action on variables that are treatable, such as uncontrolled hypertension and diabetes, concomitant use of aspirin/antiplatelet agents and overconsumption of alcohol. Using the HAS-BLED score, results in paper I demonstrated a moderate predictive accuracy (C statistics 0.63) for major bleeding events.

Furthermore, risk factors of mortality were determined in papers I and IV, which in both cohorts included age, hypertension and diabetes. In paper IV, AF, heart failure, vascular disease and renal failure were added to the independent risk factors of mortality. These risk factors appear to be as evident as in the general population, and many of the risk factors have been reported in other observational cohorts with MHV(134, 135). In spite of the well-managed warfarin treatment, there was a significant correlation between and mortality in paper IV. AF and heart failure are conditions that share common risk factors and frequently coexist where each condition predisposes to the other. The extraction of diagnoses in NPR can entail risk of missing true diagnosis of heart failure with preserved ejection fraction. Since the prevalence of AF is high in patients with heart failure, especially in patients with preserved ejection fraction (136), and the risk of death is similar to heart failure with reduced ejection fraction (137), there could be residual risk of confounding. This is acknowledged in paper I, where risk factors were much more carefully registered than in paper IV, but did not result in any correlation to mortality.

Limitations

There are several limitations in the papers that need to be acknowledged. In paper I-III, the cohorts of Malmö and Sundsvall from Auricula were obtained and included in the studies. Many of the baseline data were gathered retrospectively, which cannot exclude bias. The monitoring time did not cover the entire post cardiac surgery period for every patient, and thus different exposure times exist for each patient, although statistical adjustment was made for time since valve replacement. This cross-sectional view was also applied for paper IV. This is in contrast to the other randomized trials with MHV, where the follow-up time starts following replacement surgery. For paper I-III, the diagnosis were thoroughly investigated and validated in the medical charts by one of the authors for each center and did not dependent on diagnosis that were registered as in paper IV. Thus, patient characteristics were more reliable in these papers, whereas paper IV was contingent on diagnoses that were registered by physicians in hospitals, which was extracted from the Patient register. This included both outpatient as inpatient care, but did not cover primary care. The positive predictive values for diagnoses in the Patient Register vary between diagnoses, but are generally in the range of 85-99%(138). However, there is clearly a risk of missing true diagnosis and underestimating the risk factors, i.e. the negative predictive negative value. Since knowledge about true prevalence of diseases is required, including patients who have not yet received a diagnosis, the negative predictive value cannot be assessed. In addition, patients with many diseases may not get codes for every disease. Most of the information in the registries is binary, which may not be a problem for definite variables such as myocardial infarction or gastrointestinal bleeding, but may be a problem for diagnoses such as hypertension where treatment status and the severity are coded the same way. Furthermore, endpoints used in paper IV, could escape registration if bleeding events were cared for in the primary care, and it is likely that some endpoints were recorded as secondary diagnoses, and therefor not recorded as true endpoints. Hence, adjudication was not made for all endpoints as they were in paper I-III. Registry studies are prone to rather underestimate diagnosis and endpoints and are associated with more bias than prospective studies.

The results and design of paper I are descriptive and exploratory in nature and do not have a control group for comparison. This paper was initially thought as being solely descriptive and hypothesis generating in terms of incidence of adverse events and risk

factors relating to these. This study generated the idea of exploring the incidences and risk factors on a greater level, which resulted in paper IV.

In paper IV, the prescription of drugs such as aspirin and P2Y12-inhibitors, were extracted six months before study start with no definite awareness of the duration and concomitant use of the agents with warfarin when the study period started. Hence, these variables were not used in the multivariate analysis. Since the addition of aspirin to VKA-treatment in patients with MHV is controversial, it would have been of importance to assess the adverse events with double antithrombotic combination. The guidelines are once more discordant in adding aspirin to VKA-treatment. The AHA/ACC and ACCP guidelines suggest adding over not adding aspirin, whereas the ESC guidelines suggest that it should only be considered after full investigation and treatment of identified risk factors, and for specific indications for the shortest time possible. There were very few patients on concomitant therapy in paper I, which reflects that long-term treatment of doubled antithrombotic therapy in Sweden is rare. For this reason, assessment of this therapy could not be made.

For the cohorts in Malmö and Sundsvall, and for paper IV, we could not identify the different type and model of the MHV that were implanted. Many studies in MHV are revolved around one type and model in order to assess the thrombogenicity and the INR target studied for that particular model. Our heterogeneous material that probably consists of many different models of MHV, is however representative of clinical practice and results can more easily be implemented to daily practice. Moreover, only bileaflet valves were implanted in Sweden during the study periods in all papers.

One major limitation in paper I-III is the INR target range 2.0-4.0 that was used for all patients with MHV in the Malmö cohort during the study period. This is not supported in guidelines anymore, and there are studies showing that wide INR target ranges and INR target value of 3.0 may be to high, since bleeding risk is increased. Despite the higher comorbidity in the Malmö cohort than Sundsvall, there was a clear trend of increased major bleeding rates, which remained numerically higher in the propensity score matched cohort. The incidence of adverse events should therefor be interpreted in the context of this anticoagulation intensity when comparing to other studies. However, the widened target range facilitates the estimation of the INR variability, which is clearly higher when the target range is wide, to obtain statistical power for the association to the endpoints.

In paper II, the GFR was estimated with the revised LM equation without body and weight measure, which is not as accurate as the equation that involves body and weight measure. A relative GFR was estimated according to the body mean surface, instead of an absolute GFR, which evidently gives a more accurate measure of the renal function. There were approximately 5% of the patients that did not have measured renal function during the study period. The influence of these excluded

patients on the association to adverse events is difficult to predict, but since patients with reduced renal function have continuous contact with the health care system, this would probably imply that relatively healthy patients were excluded. This could eventually underestimate our results in paper II. Furthermore, the proportion of patients with reduced kidney function in the strata of <30 and 30-45 ml/min/1.73 m^2 were to few to establish a careful and strong statistical correlation. Thus, the results of subgroup analysis of the different eGFR strata have to be interpreted with caution.

The analysis of INR variability was made according to Fihn's variance growth rate, due to the use and validation of this formula in earlier studies(95, 96) while other studies have used standard deviation formula defining the INR variability(94). There is only a small difference in the denominator between these two equations. The results in paper III were also calculated with INR variability defined as the standard deviation, and resulted in similar associations to the adverse events. Furthermore, the measurement of INR variability would have been more robust with a larger cohort that could have yielded a more accurate threshold for distinguishing the adverse events. This could have yielded another threshold for dividing low vs. high variability. Larger cohorts are needed to reproduce our findings and investigate if the threshold within INR target ranges that are more valid would be different from ours.

To achieve balance between the observed covariates in the treatment groups in paper I and IV, propensity score matching were made. Once the propensity score is estimated, the scores can be applied in different techniques. In order to match the groups perfectly as in a randomized experiment, the individual's covariate values need to be very similar, which requires not to many covariates to control for and a large cohort. The matching process used in our cohorts included nearest neighbor matching within a specified caliper distance (0.2). Given the relatively small cohorts and many covariates to control for, it is difficult to find subjects who are similar on all covariates. Although propensity scores can be calculated with many covariates resulting in one scalar (continuous) value, some groups were not equal in the proportions. This is obviously associated with bias since difference in the measured covariates can influence treatment effect. Furthermore, within a randomized controlled trial, the randomization process minimizes the risk of differences on observed and unobserved covariates. Propensity score matching can only be controlled for measured covariates.

Conclusions

- The incidence of TE and major bleeding events in a cohort prospectively registered patients with MHV exceeds previous published studies. In spite of increase in events, the mortality rate is equal to that of the general population.
- The incidence of major bleeding is more than doubled compared to TE-events with contemporary INR target and tight anticoagulation control.
- There is an independent association of CKD with major bleeding events and death, but not with TE-events. The adjusted risk of a combined endpoint was more than 3 times higher in patients with eGFR <30 ml/min/1.73 m^2 compared to patients with normal renal function. The proportion of patients with deranged INR values increased as the eGFR decreased.
- The INR variability has an equal predictive ability as TTR 2.0-4.0 for the combined endpoint and performs even better predicting mortality. Our results indicate that the risk of suffering an event in the combined endpoint within different levels of TTR is significantly influenced by high INR variability.
- The incidence of major bleeding increases slightly when INR values are 3.0-4.0 and rises sharply when INR >4.0. The incidence of TE increases substantially when INR <1.5 and is balanced when INR >2.5. The incidence of TE in AVR and MVR seem to be similar in INR target ranges 2.0-3.0 and 2.5-3.5 in our cohort.
- Age and previous stroke are confirmed as risk factors of TE. However, risk factors such as AF and heart failure that are believed to increase the risk, did not show any correlations to increased TE in patients with well-managed warfarin-treatment. There is no evidence that these risk factors increase the risk of TE, even less that raising INR target upwards will decrease the risk of TE in well-managed patients on warfarin.

Future considerations

Following paper I and another previous study from our center, the INR target range of patients with MHV was subsequently changed according to the current guidelines recommendations. The higher intensity of the anticoagulation treatment, and in particular the wide range was associated with higher INR variability as presented in paper III. The addition of INR variability to the more adapted TTR, gives a wider spectrum of the anticoagulation treatment quality. The chairmen of Auricula are currently considering incorporating the usage of INR variability and TTR for every patient in the registry to identify patients with increased risk of adverse events. The computerized equations can visualize patients with inferior anticoagulation treatment quality to the anticoagulation clinics that can investigate the issue further. These surrogate measures of treatment quality cannot be easily assessed in the clinics and a systematic control by Auricula and anticoagulation clinics can possibly intervene in some cases, and decrease the anticoagulation-related risk of adverse events.

Another important implication of the risk of adverse events, are patients with impaired renal function. Not only do thy have deranged INR values, but the major bleeding events and death rate increases massively with decreased eGFR. A possible approach would be tighter INR control in terms of more frequent INR testing, review of concomitant medication that can interact with warfarin or directly increase the bleeding risk, and for some appropriate patients to offer self -monitoring since this method have proved to reduce INR variability.

TAVR has in the recent years become more available in patients who are at high and medium risk of conventional surgery. Recently the PARTNER 2 trial, a randomized multicenter study in intermediate-risk patients with severe aortic stenosis were randomized to TAVR or conventional surgery(139). The results showed that the rate of death or disabling stroke at two years was similar between the groups. The noninferiority of TAVR and less invasive procedure compared to conventional surgery will likely increase substantially in the intermediate risk category. Up until now, advanced age, left ventricular dysfunction or the presence of multiple coexisting conditions has been the reasons the patient cannot undergo conventional surgery. Despite that guidelines recommend MHV in the aortic position in patients <60 years of age, there is an increasing trend the past years toward implantation of surgical bioprosthesis in this age group (140). Possible contributors may be the suggested improved durability of bioprosthesis, which however is not proved yet (140, 141).

Still, the single most important factor is the avoidant of anticoagulant therapy that has likely contributed to the increase of bioprosthetic valves. The risk of SVD increases in a younger population(142), and reoperation may be needed, which commonly is treated with a surgical bioprosthesis or MHV. Hence, following current guidelines recommendation for now is probably sensible. However, due to abovementioned reasons and the introduction of TAVR, a recent study showed that the proportion of MVH decreased from 11% in 2002 to 2% in 2012 at a major German center (140). In patients between 60-70 years old, either prosthesis is acceptable according to current guidelines. One randomized trial compared older models of MHV and biological valves that resulted in no difference in long-term survival(19), whereas two other randomized trials favored MHV(20, 21). Recently, a Swedish study compared a propensity score matched cohort between 50-69 years with mechanical vs. biological prosthesis showed better long-term survival in patients who received a MHV with no difference in survival in patients between 60-69 years (22). The results are quite contradictory, since there are observational studies favoring bioprosthesis down to 50 years of age (24, 25). Current trends seem to go in the opposite direction, in particular when comparing to guideline recommendations. Owing to a considerable shift toward bioprosthesis implantation, it is expected that SVD will increase and need of reoperation is evident. The option of performing a subsequent transcatheter valve-in-valve procedure has emerged as a safe and feasible alternative, as opposed to conventional surgery. A multinational valve-in-valve registry showed recently a 1-year overall survival of 83%(143). The increasing experience of this procedure may affect cardiac surgery practice, especially as the proportion of bioprosthetic valve are increasing in younger patients. Time will tell if this trends carries on at the expense of MHV. There is however to date no clinical evidence that implantation of bioprosthesis in patients <60 years with subsequent valve-in-valve therapy is superior to implantation of MHV in terms of survival, morbidity and quality of life.

The increased major bleeding risk in patients with MHV compared to other patients with VKA-treatment could to some extent be due to AVWS. Reports have demonstrated that loss of ultra-large multimers of VWF is frequent in patients with left ventricular assist device (LVAD) (144) and in patients with severe aortic stenosis (51) with subsequent bleeding risk. Recently, it was reported that valve prosthesis dysfunction were associated with abnormalities of VWF multimers with increased incidence of bleeding (52). This finding is very interesting since the excessive bleeding risk in patients with MHV in our cohort cannot be solely explained by anticoagulation treatment and comorbidities. It would be of great importance to study the association of VFW multimers and bleeding in patients with MHV further in the future.

Populärvetenskaplig sammanfattning

Hjärtklaffssjukdomar drabbar omkring 100 miljoner människor världen över och ökar stadigt med vår allt äldre befolkning. Den vanligaste orsaken till att hjärtklaffar drabbas av sjukdom är generell åderförkalkningssjukdom som blir allt vanligare med högre ålder. Reumatisk klaffsjukdom som drabbar hjärtklaffarna efter några veckor till följd av streptokockinfektion är ytterst ovanlig i västvärlden men förekommer fortfarande i utvecklingsländer och framförallt hos yngre individer. Hjärtklaffarnas uppgift är att fungera som ventiler och hindrar blodet från att pumpas i fel riktning. Klaffsjukdomar kan delas upp i förträngningar eller läckage, eller en kombination av dessa. Fel i vänstra hjärthalvans klaffar är betydligt vanligare än höger hjärthalva. Förträngning av aortaklaffen är det vanligaste förvärvade klaffelet som medför operation hos vuxna. Förekomsten beräknas till ca två procent över 65 års ålder och till ca fyra procent över 85 års ålder.

Den vanligaste operationsmetoden är att hjärtkirurgen opererar bort den skadade klaffen och ersätter den med en klaffprotes. Klaffproteser kan bestå av mekanisk konstgjord klaff som består av metallskivor av speciellt material som öppnas och stängs av blodströmmen, eller en biologisk klaffprotes som består av biologisk vävnad från gris eller kalv och syntetiskt material. Fördelen med mekaniska klaffproteser är att de håller livet ut och att flödet blir maximalt. Nackdelen är livslång behandling med blodförtunnande läkemedel (Waran). Fördelen med biologiska klaffproteser är att de inte kräver blodförtunning men nackdelen är att de inte håller lika länge och har något försämrade flöden genom klaffen. Både internationella och nationella riktlinjer uppger att patienter under 60 år bör få mekanisk klaffprotes och att patienter över 70 år bör få biologisk klaffprotes. Vid 60-70 år kan båda klaffproteser övervägas efter att alla faktorer sammanvägts. Anledningen till att blodförtunnande behandling är nödvändig vid användande av mekaniska klaffproteser är att materialet i sig är blodproppsgenererande. Trots behandling med Waran, är risken för blodproppar inte obefintlig och som vid användande av alla blodförtunnande läkemedel finns även en risk för blödningar. Det är därför viktigt att Waranbehandlingen är välkontrollerad för att inte öka dessa risker. Effekten av Waran mäts genom hur tunt blodet är med hjälp av ett blodprov som kallas för INR. Vanligtvis är målsättningen att blodet ska vara två till tre gånger tunnare än normalt (INR 2,0-3,0) beroende på klaffmodell, klaffposition och patientrelaterade riskfaktorer. På grund av individuella variationer på hur en individ reagerar på Waran,

mäts INR-värden med jämna mellanrum för att kunna ordinera dosering utefter terapisvar. I Sverige finns AK-mottagningar (antikoagulations-mottagningar) med mångårig erfarenhet som ansvarar för den här verksamheten. Behandlings- och kvalitetseffekt kan bedömas genom andel tid som patienten befinner sig i rätt målintervall, och som kallas för TTR. Ett annat mindre vanligt kvalitetsmått på behandlingen är att beräkna variationen (svängningar) av INR-värdena över tid som kallas för INR variabilitet. Internationella riktlinjer går isär gällande rekommendationen av målintervall för INR beroende på om eventuella patientrelaterade riskfaktorer förekommer. Vid förekomst av förmaksflimmer, hjärtsvikt och tidigare stroke bör man enligt riktlinjerna öka målintervallet för patienter med mekanisk aortaklaffprotes för att minska risken för nya blodproppar/stroke. Patienter med njursjukdomar som medför varierande grad av njursvikt har i den allmänna befolkningen och hos patienter med förmaksflimmer som behandlas med Warfarin en ökad risk för stroke, allvarliga blödningar och död. Det finns dock inga publicerade resultat för patienter med njursvikt och mekaniska klaffproteser.

Syftet med avhandlingen var att klargöra förekomsten av allvarliga händelser som stroke, allvarliga blödningar och död hos patienter med mekaniska klaffproteser. Syftet var även att utvärdera den blodförtunnande behandlingens kvalitet i form av TTR och INR variabilitet, och huruvida dessa markörer kan förutse allvarliga händelser. Vidare ville vi identifiera patientrelaterade riskfaktorer till allvarliga händelser och utröna njurfunktionens roll hos patienter med mekaniska klaffproteser.

I delarbete 1 studeras alla patienter med mekanisk hjärtklaffprotes i Malmö och Sundsvall under åren 2008-2012 via databasen Auricula. Förekomsten av systemiska blodproppar/stroke var aningen högre än tidigare rapporterade studier medan blödningsrisken var avsevärt högre. Detta trots en välkontrollerad Waranbehandling med TTR på 91 % för målintervall INR 2,0-4,0. Riskfaktor för nya blodproppar/stroke var kärlsjukdom sedan tidigare, och ålder samt tidigare blödningar för nya större blödningar. Vidare jämfördes dödligheten i gruppen mot den allmänna befolkningen i Malmö och Sundsvall utan klaffprotes och Waran, som utmynnade i samma risk trots att stroke och större blödningar var relativt sett vanligt förekommande.

I delarbete 2 studeras njurfunktionens roll och association till stroke, blödningar och död i samma studiepopulation som i delarbete 1. Förekomsten av större blödningar och död ökade i takt med allt sämre njurfunktion. Det fanns en oberoende samband av större blödningar och död till minskning av njurfunktionen, men inte för stroke/systemiska blodproppar. Den justerade risken för ett sammansatt utfallsmått av stroke, större blödningar och död var tre gånger högre för patienter med gravt nedsatt njurfunktion (under 30 ml/min) jämfört med patienter med normal njurfunktion

(över 60 ml/min). Vidare var andelen rubbade INR-värden högre hos patienter med sämre njurfunktion.

I delarbete 3 studerades endast populationen i Malmö avseende INR variabilitet och TTR. Resultaten visar att INR variabilitet kan med samma precisionsgrad som TTR förutsäga risken för det sammansatta utfallsmåttet, och är dessutom mer associerad till dödlighet jämfört med TTR. Variabiliteten av INR-värdena förutsåg stroke/systemiska blodproppar bättre än TTR, medan TTR förutsåg större blödningar bättre än INR variabilitet. Vidare kunde hög INR variabilitet inom olika nivåer av TTR förutsäga risken för det sammansatta utfallsmåttet. Risken för stroke och större blödningar var lägst i INR-intervallet 2,5-3,0.

I delarbete 4 studerades en nationell population med mekaniska klaffproteser från svenska klaffregistret och Auricula avseende förekomst av stroke/systemiska blodproppar och större blödningar, samt riskfaktorer till dessa händelser. Förekomsten av stroke/systemiska blodproppar ökade svagt linjärt med åldern, medan större blödningar ökade kraftigt efter 70 års ålder. Risken för en större blödning är mer än dubbelt så hög jämfört med stroke/systemiska blodproppar för både aorta- och mitralisklaffar med rådande INR mål-intervall. Ålder och tidigare stroke var signifikanta riskfaktorer för nya händelser av stroke/systemiska blodproppar, utan någon association till förmaksflimmer eller hjärtsvikt. Ålder och tidigare blödningar var signifikanta riskfaktorer för nya händelser av större blödningar..

Avhandlingens slutsats är att förekomsten av allvarliga händelser hos patienter med mekaniska klaffproteser är högre än tidigare publicerade resultat i en modern klinisk patientgrupp trots en välkontrollerad Waranbehandling. Internationella riktlinjer är fortsatt samstämmiga kring det mest optimala mål-intervallet för patienter med riskfaktorer som tros öka risken för stroke. Vi har visat att med modern och effektiv Waranbehandling, att förekomsten av förmaksflimmer och hjärtsvikt inte ökar risken för stroke/blodproppar, och att en höjning av mål-intervallet säkerligen skulle öka risken för blödning ytterligare. Detta resultat sågs både i den mindre kohorten i Malmö och Sundsvall, och även i den nationella kohorten i delarbete 4. AK-mottagningar runt landet som är kopplade till det nationella kvalitetsregistret Auricula, kommer sannolikt inom snar framtid att kunna följa varje patients TTR och INR variabilitet för att finna de som löper högre risk för komplikationer. En annan patientgrupp som bör följas noggrant är patienter med njursvikt som dels löper högre risk för komplikationer och dels har sämre kontroll av sin Waranbehandling. I en tid där de biologiska klaffproteserna har ökat markant på bekostnad av de mekaniska klaffproteserna, och där valet mellan protestyp fortfarande är kontroversiellt i åldern 50-70 år, är våra resultat ett viktigt element i den fortsatta optimeringen av patienter med hjärtklaffsjukdomar.

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References

1. Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, Maurer G, Baumgartner H. Predictors of outcome in severe, asymptomatic aortic stenosis. N Engl J Med. 2000;343(9):611-7.
2. Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, Kraft CD, Miyake-Hull CY, et al. Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. Circulation. 1997;95(9):2262-70.
3. Edmunds LH, Jr. Evolution of prosthetic heart valves. American heart journal. 2001;141(5):849-55.
4. III BL. Prosthtetic heart valves. 1969.
5. Bokros JC. Carbon in prosthetic heart valves. The Annals of thoracic surgery. 1989;48(3 Suppl):S49-50.
6. CA Hufnagel WH, PJ Rabil. Surgical correction of aortic insufficiency. Surgery. 1954(35):673-83.
7. Starr A HR, Wood JA. Accumulated experience with the Starr-Edwards prosthesis 1960-1968. Brewer LA III, ed Prosthetic heart valves Springfield, IL_ Charles C Thomas. 1969:148-63.
8. Grunkemeier GL, Li HH, Naftel DC, Starr A, Rahimtoola SH. Long-term performance of heart valve prostheses. Curr Probl Cardiol. 2000;25(2):73-154.
9. Bjork VO. Advantages and long term results of the Bjork-Shiley valve. Verh Dtsch Ges Inn Med. 1981;87:1365-7.
10. Lindblom D, Rodriguez L, Bjork VO. Mechanical failure of the Bjork-Shiley valve. Updated follow-up and considerations on prophylactic rereplacement. J Thorac Cardiovasc Surg. 1989;97(1):95-7.
11. Blot WJ, Ibrahim MA, Ivey TD, Acheson DE, Brookmeyer R, Weyman A, Defauw J, Smith JK, et al. Twenty-five-year experience with the Bjork-Shiley convexoconcave heart valve: a continuing clinical concern. Circulation. 2005;111(21):2850-7.
12. Omar RZ, Morton LS, Beirne M, Blot WJ, Lawford PV, Hose R, Taylor KM. Outlet strut fracture of Bjork-Shiley convexo-concave valves: can valve-manufacturing characteristics explain the risk? J Thorac Cardiovasc Surg. 2001;121(6):1143-9.

13. Svennevig JL, Abdelnoor M, Nitter-Hauge S. Twenty-five-year experience with the Medtronic-Hall valve prosthesis in the aortic position: a follow-up cohort study of 816 consecutive patients. Circulation. 2007;116(16):1795-800.
14. Gott VL, Daggett RL, Young WP. Development of a carbon-coated, central-hinging, bileaflet valve. The Annals of thoracic surgery. 1989;48(3 Suppl):S28-30.
15. Emery RW, Arom KV, Kshettry VR, Kroshus TJ, Von R, Kersten TE, Lillehei TJ, Nicoloff DM, et al. Decision-making in the choice of heart valve for replacement in patients aged 60-70 years: twenty-year follow up of the St. Jude Medical aortic valve prosthesis. J Heart Valve Dis. 2002;11 Suppl 1:S37-44.
16. Moidl R, Simon P, Wolner E. The On-X prosthetic heart valve at five years. The Annals of thoracic surgery. 2002;74(4):S1312-7.
17. Chambers JB, Pomar JL, Mestres CA, Palatianos GM. Clinical event rates with the On-X bileaflet mechanical heart valve: a multicenter experience with follow-up to 12 years. J Thorac Cardiovasc Surg. 2013;145(2):420-4.
18. Edmunds LH, Jr., Cohn LH, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. J Thorac Cardiovasc Surg. 1988;96(3):351-3.
19. Oxenham H, Bloomfield P, Wheatley DJ, Lee RJ, Cunningham J, Prescott RJ, Miller HC. Twenty year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. Heart. 2003;89(7):715-21.
20. Stassano P, Di Tommaso L, Monaco M, Iorio F, Pepino P, Spampinato N, Vosa C. Aortic valve replacement: a prospective randomized evaluation of mechanical versus biological valves in patients ages 55 to 70 years. J Am Coll Cardiol. 2009;54(20):1862-8.
21. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. J Am Coll Cardiol. 2000;36(4):1152-8.
22. Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Aortic valve replacement with mechanical vs. biological prostheses in patients aged 50-69 years. Eur Heart J. 2015.
23. Brown ML, Schaff HV, Lahr BD, Mullany CJ, Sundt TM, Dearani JA, McGregor CG, Orszulak TA. Aortic valve replacement in patients aged 50 to 70 years: improved outcome with mechanical versus biologic prostheses. J Thorac Cardiovasc Surg. 2008;135(4):878-84; discussion 84.
24. McClure RS, McGurk S, Cevasco M, Maloney A, Gosev I, Wiegerinck EM, Salvio G, Tokmaji G, et al. Late outcomes comparison of nonelderly patients with stented bioprosthetic and mechanical valves in the aortic position: a propensity-matched analysis. J Thorac Cardiovasc Surg. 2014;148(5):1931-9.

25. Chiang YP, Chikwe J, Moskowitz AJ, Itagaki S, Adams DH, Egorova NN. Survival and long-term outcomes following bioprosthetic vs mechanical aortic valve replacement in patients aged 50 to 69 years. JAMA. 2014;312(13):1323-9.
26. Debetaz LF, Ruchat P, Hurni M, Fischer A, Stumpe F, Sadeghi H, van Melle G, Goy JJ. St. Jude Medical valve prosthesis: an analysis of long-term outcome and prognostic factors. J Thorac Cardiovasc Surg. 1997;113(1):134-48.
27. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation. 1994;89(2):635-41.
28. Baudet EM, Puel V, McBride JT, Grimaud JP, Roques F, Clerc F, Roques X, Laborde N. Long-term results of valve replacement with the St. Jude Medical prosthesis. J Thorac Cardiovasc Surg. 1995;109(5):858-70.
29. Hering D, Piper C, Bergemann R, Hillenbach C, Dahm M, Huth C, Horstkotte D. Thromboembolic and bleeding complications following St. Jude Medical valve replacement: results of the German Experience With Low-Intensity Anticoagulation Study. Chest. 2005;127(1):53-9.
30. Koertke H, Zittermann A, Tenderich G, Wagner O, El-Arousy M, Krian A, Ennker J, Taborski U, et al. Low-dose oral anticoagulation in patients with mechanical heart valve prostheses: final report from the early self-management anticoagulation trial II. Eur Heart J. 2007;28(20):2479-84.
31. Torella M, Torella D, Chiodini P, Franciulli M, Romano G, De Santo L, De Feo M, Amarelli C, et al. LOWERing the INtensity of oral anticoaGulant Therapy in patients with bileaflet mechanical aortic valve replacement: results from the "LOWERING-IT" Trial. Am Heart J. 2010;160(1):171-8.
32. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH, American College of Chest P. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e576S-600S.
33. Joint Task Force on the Management of Valvular Heart Disease of the European Society of C, European Association for Cardio-Thoracic S, Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, et al. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J. 2012;33(19):2451-96.
34. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, O'Gara PT, Ruiz CE, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(22):e57-185.
35. Horstkotte D, Scharf RE, Schultheiss HP. Intracardiac thrombosis: patient-related and device-related factors. J Heart Valve Dis. 1995;4(2):114-20.

36. Becker RC, Eisenberg P, Turpie AG. Pathobiologic features and prevention of thrombotic complications associated with prosthetic heart valves: fundamental principles and the contribution of platelets and thrombin. Am Heart J. 2001;141(6):1025-37.

37. Vroman L AA, Klings M. Interactions among human blood proteins at interfaces. Fed Proc. 1971(30):1494-502.

38. Vroman L, Adams AL, Fischer GC, Munoz PC. Interaction of high molecular weight kininogen, factor XII, and fibrinogen in plasma at interfaces. Blood. 1980;55(1):156-9.

39. Wessler S. Thrombosis in the presence of vascular stasis. Am J Med. 1962;33:648-66.

40. Malone PC, Morris CJ. The sequestration and margination of platelets and leucocytes in veins during conditions of hypokinetic and anaemic hypoxia: potential significance in clinical postoperative venous thrombosis. J Pathol. 1978;125(3):119-29.

41. Vink R, Kraaijenhagen RA, Hutten BA, van den Brink RB, de Mol BA, Buller HR, Levi M. The optimal intensity of vitamin K antagonists in patients with mechanical heart valves: a meta-analysis. J Am Coll Cardiol. 2003;42(12):2042-8.

42. Roudaut R, Serri K, Lafitte S. Thrombosis of prosthetic heart valves: diagnosis and therapeutic considerations. Heart. 2007;93(1):137-42.

43. Martino R, Souto JC, Mateo J, Fontcuberta J. Thrombolysis as the first line of therapy for cardiac valve thrombosis. Circulation. 1993;88(2):808-9.

44. Barbetseas J, Nagueh SF, Pitsavos C, Toutouzas PK, Quinones MA, Zoghbi WA. Differentiating thrombus from pannus formation in obstructed mechanical prosthetic valves: an evaluation of clinical, transthoracic and transesophageal echocardiographic parameters. J Am Coll Cardiol. 1998;32(5):1410-7.

45. Lengyel M, Fuster V, Keltai M, Roudaut R, Schulte HD, Seward JB, Chesebro JH, Turpie AG. Guidelines for management of left-sided prosthetic valve thrombosis: a role for thrombolytic therapy. Consensus Conference on Prosthetic Valve Thrombosis. J Am Coll Cardiol. 1997;30(6):1521-6.

46. Roskell NS, Samuel M, Noack H, Monz BU. Major bleeding in patients with atrial fibrillation receiving vitamin K antagonists: a systematic review of randomized and observational studies. Europace. 2013;15(6):787-97.

47. Puskas J, Gerdisch M, Nichols D, Quinn R, Anderson C, Rhenman B, Fermin L, McGrath M, et al. Reduced anticoagulation after mechanical aortic valve replacement: interim results from the prospective randomized on-X valve anticoagulation clinical trial randomized Food and Drug Administration investigational device exemption trial. J Thorac Cardiovasc Surg. 2014;147(4):1202-10; discussion 10-1.

48. Mecozzi G, Milano AD, De Carlo M, Sorrentino F, Pratali S, Nardi C, Bortolotti U. Intravascular hemolysis in patients with new-generation prosthetic heart valves: a prospective study. J Thorac Cardiovasc Surg. 2002;123(3):550-6.

49. Liu JS, Lu PC, Chu SH. Turbulence characteristics downstream of bileaflet aortic valve prostheses. J Biomech Eng. 2000;122(2):118-24.

50. Heyde E. Gastrointestinal bleeding in aortic stenosis (Letter). New England Journal of Medicine. 1958;259(196).
51. Vincentelli A, Susen S, Le Tourneau T, Six I, Fabre O, Juthier F, Bauters A, Decoene C, et al. Acquired von Willebrand syndrome in aortic stenosis. N Engl J Med. 2003;349(4):343-9.
52. Blackshear JL, McRee CW, Safford RE, Pollak PM, Stark ME, Thomas CS, Rivera CE, Wysokinska EM, et al. von Willebrand Factor Abnormalities and Heyde Syndrome in Dysfunctional Heart Valve Prostheses. JAMA Cardiol. 2016;1(2):198-204.
53. Van Belle E, Rauch A, Vincent F, Robin E, Kibler M, Labreuche J, Jeanpierre E, Levade M, et al. Von Willebrand Factor Multimers during Transcatheter Aortic-Valve Replacement. New England Journal of Medicine. 2016;375(4):335-44.
54. Kortke H, Korfer R. International normalized ratio self-management after mechanical heart valve replacement: is an early start advantageous? The Annals of thoracic surgery. 2001;72(1):44-8.
55. Butchart EG, Payne N, Li HH, Buchan K, Mandana K, Grunkemeier GL. Better anticoagulation control improves survival after valve replacement. J Thorac Cardiovasc Surg. 2002;123(4):715-23.
56. Shapiro SS. Treating Thrombosis in the 21st Century. New England Journal of Medicine. 2003;349(18):1762-4.
57. Morawitz P. Die Chemie der Blutgerinnung. Ergeb Physiol. 1905;4:307–422.
58. AJ Patek RS. Hemophilia. I. The abnormal coagulation of the blood and its relation to the blood platelets. J Clin Invest. 1936;15:531–42.
59. Wright IS. Concerning the Functions and Nomenclature of Blood Clotting Factors. Trans Am Clin Climatol Assoc. 1959;70:67-74.
60. AJ Quick MSB, FW Bancroft. A study of the coagulation defect in hemophilia and in jaundice. Am J Med Sci. 1935;190:501-11.
61. EW Davie OR. Waterfall sequence of for intrinsic blood coagulation. Science. 1964;145:1310-2.
62. Macfarlane R. An enzyme cascade in the blood coagulation mechanism, and its function as a biochemical amplifier. Nature (Lond). 1964;202:498-9.
63. Egeberg O. Inherited Antithrombin Deficiency Causing Thrombophilia. Thromb Diath Haemorrh. 1965;13:516-30.
64. Griffin JH, Evatt B, Zimmerman TS, Kleiss AJ, Wideman C. Deficiency of protein C in congenital thrombotic disease. J Clin Invest. 1981;68(5):1370-3.
65. PC Comp RN, MR Cooper, CT Esmon. Familiar protein S deficiency is associated with recurrent thrombosis. J Clin Invest. 1984;74:2082-8.
66. Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, van der Velden PA, Reitsma PH. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature. 1994;369(6475):64-7.

67. The National Board of Health and Welfare (Socialstyrelsen) [cited 2015]. Available from: http://www.socialstyrelsen.se/statistik/statistikdatabas/lakemedel.
68. Heemskerk JW, Bevers EM, Lindhout T. Platelet activation and blood coagulation. Thromb Haemost. 2002;88(2):186-93.
69. Hoffman M, Monroe DM, 3rd. A cell-based model of hemostasis. Thromb Haemost. 2001;85(6):958-65.
70. Dahlback B. Blood coagulation. Lancet. 2000;355(9215):1627-32.
71. Monroe DM, Hoffman M, Roberts HR. Transmission of a procoagulant signal from tissue factor-bearing cell to platelets. Blood Coagul Fibrinolysis. 1996;7(4):459-64.
72. Oliver JA, Monroe DM, Roberts HR, Hoffman M. Thrombin activates factor XI on activated platelets in the absence of factor XII. Arterioscler Thromb Vasc Biol. 1999;19(1):170-7.
73. van der Meijden PE, Munnix IC, Auger JM, Govers-Riemslag JW, Cosemans JM, Kuijpers MJ, Spronk HM, Watson SP, et al. Dual role of collagen in factor XII-dependent thrombus formation. Blood. 2009;114(4):881-90.
74. Renne T, Gailani D. Role of Factor XII in hemostasis and thrombosis: clinical implications. Expert Rev Cardiovasc Ther. 2007;5(4):733-41.
75. von Bruhl ML, Stark K, Steinhart A, Chandraratne S, Konrad I, Lorenz M, Khandoga A, Tirniceriu A, et al. Monocytes, neutrophils, and platelets cooperate to initiate and propagate venous thrombosis in mice in vivo. J Exp Med. 2012;209(4):819-35.
76. Choi SH, Smith SA, Morrissey JH. Polyphosphate is a cofactor for the activation of factor XI by thrombin. Blood. 2011;118(26):6963-70.
77. Price GC, Thompson SA, Kam PC. Tissue factor and tissue factor pathway inhibitor. Anaesthesia. 2004;59(5):483-92.
78. Ezihe-Ejiofor JA, Hutchinson N. Anticlotting mechanisms 1: physiology and pathology. Continuing Education in Anaesthesia, Critical Care & Pain. 2013.
79. Fulcher CA, Gardiner JE, Griffin JH, Zimmerman TS. Proteolytic inactivation of human factor VIII procoagulant protein by activated human protein C and its analogy with factor V. Blood. 1984;63(2):486-9.
80. Cesarman-Maus G, Hajjar KA. Molecular mechanisms of fibrinolysis. Br J Haematol. 2005;129(3):307-21.
81. A Q. The prothrombin time in hemophilia and in obstructive jaundice. J Biol Chem. 1935;109:73-4.
82. Owren PA, Aas K. The control of dicumarol therapy and the quantitative determination of prothrombin and proconvertin. Scand J Clin Lab Invest. 1951;3(3):201-8.
83. Owren PA. Thrombotest. A new method for controlling anticoagulant therapy. Lancet. 1959;2(7106):754-8.
84. WHO. Expert Committee on Biological Standardisation 33th Report. WHO technical Report series1983. p. 81-105.

85. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. Arch Intern Med. 1987;147(9):1561-4.

86. European Heart Rhythm A, European Association for Cardio-Thoracic S, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010;31(19):2369-429.

87. White HD, Gruber M, Feyzi J, Kaatz S, Tse HF, Husted S, Albers GW. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. Arch Intern Med. 2007;167(3):239-45.

88. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993;69(3):236-9.

89. Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, Bankhead C, Xu Y. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. Circ Cardiovasc Qual Outcomes. 2008;1(2):84-91.

90. Sanden P, Renlund H, Svensson PJ, Sjalander A. Warfarin treatment complications do not correlate to cTTR when above 70. Thromb Res. 2015;136(6):1185-9.

91. Fihn SD, McDonell M, Martin D, Henikoff J, Vermes D, Kent D, White RH. Risk factors for complications of chronic anticoagulation. A multicenter study. Warfarin Optimized Outpatient Follow-up Study Group. Ann Intern Med. 1993;118(7):511-20.

92. Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJ, Vandenbroucke JP, Briet E. Optimal oral anticoagulant therapy in patients with mechanical heart valves. N Engl J Med. 1995;333(1):11-7.

93. Fihn SD, Callahan CM, Martin DC, McDonell MB, Henikoff JG, White RH. The risk for and severity of bleeding complications in elderly patients treated with warfarin. The National Consortium of Anticoagulation Clinics. Ann Intern Med. 1996;124(11):970-9.

94. Lind M, Fahlen M, Kosiborod M, Eliasson B, Oden A. Variability of INR and its relationship with mortality, stroke, bleeding and hospitalisations in patients with atrial fibrillation. Thromb Res. 2012;129(1):32-5.

95. Razouki Z, Ozonoff A, Zhao S, Jasuja GK, Rose AJ. Improving quality measurement for anticoagulation: adding international normalized ratio variability to percent time in therapeutic range. Circ Cardiovasc Qual Outcomes. 2014;7(5):664-9.

96. van Leeuwen Y, Rosendaal FR, Cannegieter SC. Prediction of hemorrhagic and thrombotic events in patients with mechanical heart valve prostheses treated with oral anticoagulants. J Thromb Haemost. 2008;6(3):451-6.

97. Nyman U, Grubb A, Larsson A, Hansson LO, Flodin M, Nordin G, Lindstrom V, Bjork J. The revised Lund-Malmo GFR estimating equation outperforms MDRD and CKD-EPI across GFR, age and BMI intervals in a large Swedish population. Clin Chem Lab Med. 2014;52(6):815-24.

98. Bjork J, Jones I, Nyman U, Sjostrom P. Validation of the Lund-Malmo, Chronic Kidney Disease Epidemiology (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) equations to estimate glomerular filtration rate in a large Swedish clinical population. Scand J Urol Nephrol. 2012;46(3):212-22.
99. Methods to Estimate and Measure Renal Function (Glomerular Filtration Rate): A Systematic Review. SBU Systematic Review Summaries. Stockholm2011.
100. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-305.
101. Marinigh R, Lane DA, Lip GY. Severe renal impairment and stroke prevention in atrial fibrillation: implications for thromboprophylaxis and bleeding risk. J Am Coll Cardiol. 2011;57(12):1339-48.
102. Herzog CA, Ma JZ, Collins AJ. Long-term survival of dialysis patients in the United States with prosthetic heart valves: should ACC/AHA practice guidelines on valve selection be modified? Circulation. 2002;105(11):1336-41.
103. Umezu K, Saito S, Yamazaki K, Kawai A, Kurosawa H. Cardiac valvular surgery in dialysis patients: comparison of surgical outcome for mechanical versus bioprosthetic valves. Gen Thorac Cardiovasc Surg. 2009;57(4):197-202.
104. Chan V, Jamieson WR, Fleisher AG, Denmark D, Chan F, Germann E. Valve replacement surgery in end-stage renal failure: mechanical prostheses versus bioprostheses. The Annals of thoracic surgery. 2006;81(3):857-62.
105. Yearly Report Auricula 2015. Available from: http://www.ucr.uu.se/auricula/index.php/arsrapporter/doc_download/53-auricula-arsrapport-2014.
106. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, Takkenberg JJ, David TE, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. Eur J Cardiothorac Surg. 2008;33(4):523-8.
107. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3(4):692-4.
108. Bjork J, Grubb A, Sterner G, Nyman U. Revised equations for estimating glomerular filtration rate based on the Lund-Malmo Study cohort. Scand J Clin Lab Invest. 2011;71(3):232-9.
109. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behavioral Research. 2011;46(3):399-424.
110. Thoemmes F. Propensity score matching in SPSS 2012. Available from: http://arxiv.org/pdf/1201.6385v1.pdf.

111. Jernberg T, Attebring MF, Hambraeus K, Ivert T, James S, Jeppsson A, Lagerqvist B, Lindahl B, et al. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). Heart. 2010;96(20):1617-21.

112. Acar J, Iung B, Boissel JP, Samama MM, Michel PL, Teppe JP, Pony JC, Breton HL, et al. AREVA: multicenter randomized comparison of low-dose versus standard-dose anticoagulation in patients with mechanical prosthetic heart valves. Circulation. 1996;94(9):2107-12.

113. Horstkotte D, Schulte HD, Bircks W, Strauer BE. Lower intensity anticoagulation therapy results in lower complication rates with the St. Jude Medical prosthesis. J Thorac Cardiovasc Surg. 1994;107(4):1136-45.

114. Perez-Rodriguez A, Pinto JC, Loures E, Rodriguez-Trillo A, Cuenca JJ, Batlle J, Lopez-Fernandez MF. Acquired von Willebrand syndrome and mitral valve prosthesis leakage. A pilot study. Eur J Haematol. 2011;87(5):448-56.

115. Gadisseur AP, van der Meer FJ, Adriaansen HJ, Fihn SD, Rosendaal FR. Therapeutic quality control of oral anticoagulant therapy comparing the short-acting acenocoumarol and the long-acting phenprocoumon. Br J Haematol. 2002;117(4):940-6.

116. Torn M, Cannegieter SC, Bollen WL, van der Meer FJ, van der Wall EE, Rosendaal FR. Optimal level of oral anticoagulant therapy for the prevention of arterial thrombosis in patients with mechanical heart valve prostheses, atrial fibrillation, or myocardial infarction: a prospective study of 4202 patients. Arch Intern Med. 2009;169(13):1203-9.

117. Fang MC, Go AS, Hylek EM, Chang Y, Henault LE, Jensvold NG, Singer DE. Age and the risk of warfarin-associated hemorrhage: the anticoagulation and risk factors in atrial fibrillation study. J Am Geriatr Soc. 2006;54(8):1231-6.

118. Friberg L, Benson L, Lip GY. Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study. Eur Heart J. 2015;36(5):297-306.

119. Carrero JJ, Evans M, Szummer K, Spaak J, Lindhagen L, Edfors R, Stenvinkel P, Jacobson SH, et al. Warfarin, kidney dysfunction, and outcomes following acute myocardial infarction in patients with atrial fibrillation. JAMA. 2014;311(9):919-28.

120. Apostolakis S, Guo Y, Lane DA, Buller H, Lip GY. Renal function and outcomes in anticoagulated patients with non-valvular atrial fibrillation: the AMADEUS trial. Eur Heart J. 2013;34(46):3572-9.

121. Olesen JB, Lip GY, Kamper AL, Hommel K, Kober L, Lane DA, Lindhardsen J, Gislason GH, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med. 2012;367(7):625-35.

122. Dahal K, Kunwar S, Rijal J, Schulman P, Lee J. Stroke, Major Bleeding and Mortality Outcomes in Warfarin Users with Atrial Fibrillation and Chronic Kidney Disease: A Meta-analysis of Observational Studies. Chest. 2015.

123. Wieloch M, Sjalander A, Frykman V, Rosenqvist M, Eriksson N, Svensson PJ. Anticoagulation control in Sweden: reports of time in therapeutic range, major bleeding, and thrombo-embolic complications from the national quality registry AuriculA. Eur Heart J. 2011;32(18):2282-9.
124. Wieloch M, Jonsson KM, Sjalander A, Lip GY, Eriksson N, Svensson PJ. Estimated glomerular filtration rate is associated with major bleeding complications but not thromboembolic events, in anticoagulated patients taking warfarin. Thromb Res. 2013;131(6):481-6.
125. Limdi NA, Beasley TM, Baird MF, Goldstein JA, McGwin G, Arnett DK, Acton RT, Allon M. Kidney function influences warfarin responsiveness and hemorrhagic complications. J Am Soc Nephrol. 2009;20(4):912-21.
126. Jalal DI, Chonchol M, Targher G. Disorders of hemostasis associated with chronic kidney disease. Semin Thromb Hemost. 2010;36(1):34-40.
127. Lutz J, Menke J, Sollinger D, Schinzel H, Thurmel K. Haemostasis in chronic kidney disease. Nephrol Dial Transplant. 2014;29(1):29-40.
128. Misawa Y. Heart valve replacement for patients with end-stage renal disease in Japan. Ann Thorac Cardiovasc Surg. 2010;16(1):4-8.
129. Tantisattamo E, Han KH, O'Neill WC. Increased vascular calcification in patients receiving warfarin. Arterioscler Thromb Vasc Biol. 2015;35(1):237-42.
130. Dauphin C, Legault B, Jaffeux P, Motreff P, Azarnoush K, Joly H, Geoffroy E, Aublet-Cuvelier B, et al. Comparison of INR stability between self-monitoring and standard laboratory method: preliminary results of a prospective study in 67 mechanical heart valve patients. Arch Cardiovasc Dis. 2008;101(11-12):753-61.
131. Grzymala-Lubanski B, Labaf A, Englund E, Svensson PJ, Sjalander A. Mechanical heart valve prosthesis and warfarin - treatment quality and prognosis. Thromb Res. 2014;133(5):795-8.
132. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138(5):1093-100.
133. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, Singer DE. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. J Am Coll Cardiol. 2011;58(4):395-401.
134. Tjang YS, van Hees Y, Korfer R, Grobbee DE, van der Heijden GJ. Predictors of mortality after aortic valve replacement. Eur J Cardiothorac Surg. 2007;32(3):469-74.
135. Bouhout I, Stevens LM, Mazine A, Poirier N, Cartier R, Demers P, El-Hamamsy I. Long-term outcomes after elective isolated mechanical aortic valve replacement in young adults. J Thorac Cardiovasc Surg. 2014;148(4):1341-6 e1.

136. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med. 2006;355(3):260-9.

137. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007;50(8):768-77.

138. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.

139. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2016;374(17):1609-20.

140. Silaschi M, Conradi L, Treede H, Reiter B, Schaefer U, Blankenberg S, Reichenspurner H. Trends in Surgical Aortic Valve Replacement in More Than 3,000 Consecutive Cases in the Era of Transcatheter Aortic Valve Implantations. Thorac Cardiovasc Surg. 2015.

141. Brown JM, O'Brien SM, Wu C, Sikora JA, Griffith BP, Gammie JS. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. J Thorac Cardiovasc Surg. 2009;137(1):82-90.

142. Weber A, Noureddine H, Englberger L, Dick F, Gahl B, Aymard T, Czerny M, Tevaearai H, et al. Ten-year comparison of pericardial tissue valves versus mechanical prostheses for aortic valve replacement in patients younger than 60 years of age. J Thorac Cardiovasc Surg. 2012;144(5):1075-83.

143. Dvir D, Webb JG, Bleiziffer S, Pasic M, Waksman R, Kodali S, Barbanti M, Latib A, et al. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. JAMA. 2014;312(2):162-70.

144. Uriel N, Pak SW, Jorde UP, Jude B, Susen S, Vincentelli A, Ennezat PV, Cappleman S, et al. Acquired von Willebrand syndrome after continuous-flow mechanical device support contributes to a high prevalence of bleeding during long-term support and at the time of transplantation. J Am Coll Cardiol. 2010;56(15):1207-13.

Paper I

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Regular Article

Thromboembolism, major bleeding and mortality in patients with mechanical heart valves- a population-based cohort study☆

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ABSTRACT

Introduction: Low incidences of thromboembolism (TE) and bleeding in patients with mechanical heart valves (MHV) have previously been reported. This study assesses the incidence of and clinical risk factors predicting TE, major bleeding and mortality in a clinical setting.
Methods and results: All 546 patients undergoing anticoagulation treatment due to MHV replacement at hospitals in Malmö and Sundsvall in Sweden were monitored during 2008–2011 and the incidence of TE, major bleeding and mortality was prospectively followed. There were 398, 122 and 26 patients in the aortic group (AVR), mitral (MVR) group and the combined aortic/mitral valve group respectively. The incidence of TE was 1.8 and 2.2 per 100 patient-years in the AVR group MVR group respectively. The corresponding incidences of bleeding were 4.4 and 4.6, respectively. Independent predictor of thromboembolism was vascular disease (Odds ratio {OR}: 4.2; 95% CI: 1.0-17.4). Predictor of bleeding was previous bleeding (OR: 2.7; 95% CI: 1.4-5.3). Independent predictors of mortality was age (Hazard ratio {HR}: 1.03; 95% CI: 1.00-1.05), hypertension (HR: 2.4; 95% CI: 1.3-4.5), diabetes (HR: 2.4; 95% CI: 1.3-4.3) and alcohol overconsumption (HR: 5.2; 95% CI: 1.7-15.9). Standardized mortality/morbidity ratio for mortality and AMI was 0.99 (95% CI: 0.8-1.2) and 0.87 (95% CI: 0.5-1.2) respectively.
Conclusion: The incidence of TE and major bleeding in this unselected clinical population exceeds that of previously reported retrospective and randomized trials. Despite this, mortality is equal to that of the general population.

Introduction

Mechanical heart valves (MHV) are more durable than bioprosthetic valves; however, their use necessitates lifelong oral anticoagulation with vitamin K antagonist due to the thrombogenicity of the valve. In addition to the basic design of the valve, various patient-related risk factors are thought to influence the incidence of thromboembolism (TE) [1,2]. Depending on these variables, the American and European guidelines suggest different international normalized ratio (INR) target ranges for different patients [3–5]. As there is a lack of larger randomized prospective trials, the guidelines rely on only level B and C evidence, which is one reason why the guidelines differ in the various recommendations. Recently, the phase II RE-ALIGN study showed that treatment with dabigatran etexilate resulted in a higher number of TE and bleeding complications in patients with MHV than did treatment with warfarin [6].

The assessment of the reports regarding TE and major bleeding is made more difficult due to heterogeneous results based on differing systems for reporting complications, valve types, target INR ranges, quality of anticoagulation, length of monitoring period, total patient-years and particularly patients that are included in the studies. Despite this and the moderate anticoagulation quality, the risk of TE and bleeding have been reported at only 0.2-1.5% and 1-2.5% per year, respectively [7–12]. The definition of bleeding and thromboembolism in some studies have not been strictly followed according to the specific guidelines for reporting mortality and morbidity after cardiac valve intervention [13] which makes comparisons somewhat difficult.

Mortality data in patients with MHV compared to bioprosthetic valves have showed varying results recently [7,14,15], although data points towards better survival with MHV. Our goal was to assess the

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incidence of TE, major bleeding and mortality in all patients with MHV from a cross-sectional point of view in a clinical setting at two anticoagulation centres in Sweden. We also sought to identify the clinical risk factors predicting TE, major bleeding and mortality, and to compare the risk of mortality and acute myocardial infarction (AMI) with the general population without MHV.

Methods

Subjects

This is a population-based study that took place at two centres, the hospitals in Malmö and Sundsvall in Sweden, from 01/01/2008 until 31/12/2011. All of the patients with MHV that were on oral anticoagulation treatment during the study period at these centres were monitored in the Swedish national quality registry for atrial fibrillation and anticoagulation, AuriculA. AuriculA was introduced prior to 2008 at our centres and now contains over 110,000 patients in 224 centers throughout Sweden. The registry includes a web-based dosing program and decision support that uses an algorithm to calculate warfarin dosage based on the last two INR results [16]. When using the dosing system, quality parameters are automatically registered. The primary endpoints, major bleeding and thromboembolic events, are recorded prospectively and are requested at the end of each dosing period or annually. All events registered in this study were retrospectively validated at each centre by one of the authors who evaluated the complete medical records to confirm the diagnosis and to identify further complications. This methodology ensures that every patient with MHV is included. Cases where a decision was made to discontinue the warfarin treatment of terminal patients in the end-stages of various diseases are reported, but not accounted for in the analysis. The target INR range for all patients during the study period was 2.0-4.0 in Malmö, and 2.0-3.0 for the aortic valve group (AVR) and 2.5-3.5 for the mitral group (MVR) in Sundsvall.

Study Definitions

Demographic data such as age, sex, position of the MHV and all INR measurements were extracted from AuriculA. A large number of baseline characteristics and demographics were examined using the complete medical records, including the confirmation of major bleeding and thromboembolic events that took place during the study period 01/01/2008–31/12/2011. TE was defined according to the guidelines for reporting mortality and morbidity after cardiac valve intervention [13], i.e. stroke, transient ischemic attack (TIA) or an embolus documented operatively, at autopsy, or clinically that produces signs or symptoms attributable to complete or partial obstruction of a peripheral artery. Major bleeding events were defined according to ISTH definitions [17]. This included falls in haemoglobin levels of greater than 20 g/L, transfusion of $\geq$2 units, symptomatic bleeding in a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, as well as intramuscular with compartment syndrome) or fatal bleeding. The ISTH definition is quite similar to the guidelines for cardiac valve intervention and chosen due to its comprehensive use since. Secondary outcome was AMI and was defined as a rise and/or fall in cardiac biomarker values above the reference limit with typical ECG changes and/or symptoms of ischaemia.

Valve-related mortality is any death caused by structural valve deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event or operated valve endocarditis. Cardiac death includes all deaths resulting from cardiac causes, including valve-related deaths [13]. All mortality data was extracted from Auricula or medical journals and in a few cases from the Swedish Cause of Death Register. Patients contributed with time at risk as long as they were receiving warfarin and contribution of more than one event was permitted. TTR was calculated for every patient according to Roosendaal's method [18]. Written information letters, explaining the purpose and context of the study, were sent to every patient. The study was approved by the Regional Ethical Review Board in Lund (EPN 2012/130).

Statistical Analysis

Categorical data were described by percentages and compared using the chi-square test, and Student's t-test was used for continuous data. Incidence rates are expressed as number of events per person-time with corresponding 95% confidence intervals. Multivariate logistic regression analysis was used to identify risk factors associated with TE and major bleeding. Hazard ratios were estimated using Cox proportional-hazards regression models for survival analysis, using time since valve replacement as the time variable. Standardized mortality/morbidity ratios were calculated by the observed number of deaths and AMIs in the Malmö and Sundsvall populations based on sex and age-specific rates of 5 years and were compared with the risk of the cohort. All tests were performed two-tailed, and a p-value $<$ 0.05 was considered significant. All analyses were performed using SPSS Statistics (Version 21; SPSS Inc., IBM Corporation, NY, USA).

Results

In total there were 546 patients, with 398 patients in the AVR group, 122 in the MVR group and 26 in the combined aortic/mitral valve replacement group, and an accrued total of 1901 patient-years of monitoring. Median time for valve replacement was 2001. Baseline patient characteristics of all the patients are shown in Table 1. Time in therapeutic range (TTR) was 91.8% in Malmö for the target INR range of 2.0-4.0 and 76.2% in Sundsvall for the target INR range of 2.0-3.0. For the patients in Malmö, the TTR for the target INR range of 2.0-3.0 was estimated at 68.8%. The achieved mean (SD) INR in Malmö was 2.86 ($\pm$0.89) and 2.89 ($\pm$0.92) for AVR and MVR respectively, and in Sundsvall 2.60 ($\pm$0.63) and 2.72 ($\pm$0.86) for AVR and MVR respectively.

The cohort in Malmö was older and had more comorbidities than Sundsvall. Mean age were 70 (SD 14) and 61 (SD 14), mitral valve replacement 27% vs 9%, heart failure 30% vs 17%, vascular disease 4%

Table 1
Baseline patient characteristics.

	AVR (n = 398)	MVR (n = 122)	AVR + MVR (n = 26)
Mean age, yr	67.8 ± 14	68.6 ± 15	66 ± 17
Male gender	273 (69)	57 (47)	9 (35)
Asc Ao replacement [a]	80 (20)	2 (2)	1 (4)
Hypertension	256 (64)	76 (62)	16 (62)
Diabetes	50 (13)	23 (19)	3 (12)
Atrial fibrillation	112 (28)	81 (66)	19 (73)
Permanent	75 (19)	56 (46)	11 (42)
Paroxysmal	37 (9)	25 (21)	8 (31)
Heart failure	97 (25)	48 (39)	9 (35)
LVEF [b] (35-50%)	80 (20)	43 (35)	9 (35)
LVEF (<35%)	17 (4)	5 (4)	0
Not known	48 (12)	15 (12)	4 (15)
Vascular disease [c]	13 (3)	4 (3)	1 (4)
Previous major bleeding	43 (11)	11 (9)	3 (12)
Previous myocardial infarction	60 (15)	19 (16)	4 (15)
Previous stroke	43 (11)	21 (17)	2 (8)
Previous venous TE	5 (1)	2 (2)	3 (12)
Alcohol overconsumption [d]	8 (2)	3 (3)	0
Antiplatelet/NSAID [e]	9 (2)	3 (3)	0
Kidney failure [f]	10 (3)	6 (5)	2 (8)
Liver failure [g]	6 (2)	1 (1)	0

Values are presented as mean ± SD or n (%). [a] Concomitant ascending aorta replacement surgery; [b] Left ventricle ejection fraction; [c] Peripheral arterial disease or aortic plaque; [d] ≥ 8 Units/week; [e] Non-steroidal anti-inflammatory drugs; [f] Serum creatinine ≥ 200 μm/L; [g] Chronic hepatic disease or bilirubin > x 2 upper limit of normal in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase > x 3 upper limit of normal.

Table 2
Incidence of TE, AMI and valve thrombosis by valve position.

	All prostheses		AVR[a]		MVR[b]		AVR/MVR	
	Absolute incidence	Incidence*	Absolute incidence	Incidence*	Absolute incidence	Incidence*	Absolute incidence	Incidence*
Valve thrombosis	1	0.05 (0.003-0.3)			1	0.2 (0.01-1.2)		
Peripheral TE[c]	3	0.2 (0.04-0.4)	2	0.1 (0.02-0.5)	1	0.2 (0.01-1.2)		
Stroke/TIA	32	1.7 (1.2-2.3)	23	1.6 (1.1-2.4)	8	1.9 (0.9-3.7)	1	1.2 (0.06-5.7)
AMI[d]	26	1.4 (0.9-2.0)	17	1.2 (0.7-1.9)	8	1.9 (0.9-3.7)	1	1.2 (0.06-5.7)
All TE including AMI	**62**	**3.3 (2.5-4.2)**	**42**	**3.0 (2.2-4.0)**	**17**	**4.1 (2.5-6.4)**	**2**	**2.3 (0.4-7.7)**
All TE	**35**	**1.8 (1.3-2.5)**	**25**	**1.8 (1.2-2.6)**	**9**	**2.2 (1.1-4.0)**	**1**	**1.2 (0.06-5.7)**

*Incidence (95% CI); per 100 patient-years, [a] Aortic valve replacement, [b] Mitral valve replacement, [c] Thromboembolism, [d] Acute myocardial infarction.

vs 1%, hypertension 60% vs 74%, previous myocardial infarction 18% vs 6%, previous bleeding 13% vs 4% and kidney failure 4% vs 1% in Malmö and Sundsvall respectively.

Thromboembolism

The total number and incidence rates of TE and thrombosis for the different valves are shown in Table 2. A total of 35 TEs (1.8 per 100 patient-years) occurred. There was one single valve thrombosis in the MVR group that resulted in a redo valve surgery.

The total incidence rate and all the different types of TE were more common in the MVR group than the AVR group. However, there was no statistical difference between the groups and neither for valve-related mortality. The majority of the cohort received their replacement valves prior to 2008 with 75 patients being enrolled during the study period. There was no statistical difference between the group that received their replacement valves prior to 2008 and the group that received their replacement valves during the study period with regards to the incidence of TE and major bleeding. The incidence of TE in Malmö and Sundsvall was 2.0 (95% CI; 1.3-2.9) and 1.4 (95% CI; 0.6-2.8) per 100 patient-years respectively, $p = 0.47$.

Major Bleeding

A total of 77 patients suffered 81 events of major bleeding, corresponding to 4.3 per 100 patient-years, as shown in Table 3. Three patients suffered more than one event. The incidence of major bleeding in Malmö and Sundsvall was 5.2 (95% CI; 4.1-6.5) and 1.8 (95% CI; 0.8-3.3) per 100 patient-years respectively, $p < 0.001$.

Predictors of Thromboembolism and Major Bleeding

The different patient characteristics between those who suffered and those who did not suffer TEs for all patients with MHV are shown in Table 4, and for major bleeding in Table 5. Due to important clinical relevance of AMI, another multivariate analysis were performed for predictors of TE and AMI combined. Independent predictors were heart failure (Odds ratio {OR}: 2.42; 95% CI: 1.2-4.8), previous acute myocardial infarction (OR: 2.2; 95% CI: 1.1-4.6) and vascular disease (OR: 3.9; 95% CI: 1.2-12.4).

Few of the variables indicate trends toward univariate association with TE. Seven patients in the group who suffered a thrombotic event had received an antiplatelet drug, in addition to warfarin, for a limited

Table 3
Incidence of major bleeding by valve position.

	All prostheses		**AVR[a]**		**MVR[b]**		**AVR/MVR**	
	Absolute incidence	Incidence*	Absolute incidence	Incidence*	Absolute incidence	Incidence*	Absolute incidence	Incidence*
Cerebral bleeding	16	0.8 (0.5-1.3)	11	0.8 (0.4-1.4)	5	1.2 (0.4-2.7)	0	
Gastrointestinal bleeding	30	1.6 (1.1-2.2)	23	1.6 (1.0-2.4)	7	1.7 (0.7-3.3)	0	
Other	35	1.8 (1.3-2.5)	27	1.9 (1.3-2.8)	7	1.7 (0.7-3.3)	1	1.2 (0.06-5.7)
Fatal bleeding	5	0.3 (0.1-0.6)	5	0.4 (0.1-0.8)	0		0	
All bleeds	**81**	**4.3 (3.4-5.3)**	**61**	**4.4 (3.4-5.6)**	**19**	**4.6 (2.9-7.1)**	**1**	**1.2 (0.06-5.7)**

*Incidence (95% CI); per 100 patient-years, [a] Aortic valve replacement, [b] Mitral valve replacement.

Table 4
Multivariate logistic regression: Independent predictors of thromboembolism.

All prostheses; TE	N = 33 (%)	N = 513 (%)			
	TE	Non-TE	P-value, univariate	P-value, multivariate	Odds ratio (95% CI)
Mitral valve	9 (28)	113 (23)	0.5	0.4	1.49 (0.61-3.64)
Age > 75	11 (33)	171 (33)	1.0	0.8	0.89 (0.37-2.15)
Female	11 (33)	196 (38)	0.6	0.4	0.72 (0.31-1.65)
Asc Ao replacement [a]	3 (9)	80 (16)	0.3	0.4	0.56 (0.16-1.97)
Hypertension	23 (70)	325 (63)	0.5	0.6	1.27 (0.57-2.85)
Diabetes	4 (12)	72 (14)	0.8	0.5	0.68 (0.21-2.16)
Previous Stroke/TIA [b]	5 (15)	61 (12)	0.6	0.9	1.05 (0.33-3.32)
Heart failure [c]	10 (30)	144 (28)	0.8	1.0	1.00 (0.41-2.46)
Previous bleeding	2 (6)	55 (11)	0.4	0.5	0.60 (0.13-2.70)
Previous AMI [d]	5 (15)	78 (15)	1.0	0.9	0.91 (0.32-2.63)
Alcohol over consumption	1 (3)	10 (2)	0.7	0.9	1.19 (0.13-10.6)
Atrial fibrillation	12 (36)	200 (39)	0.8	0.6	0.81 (0.34-1.92)
Vascular disease	3 (9)	15 (3)	0.05	0.047	**4.21 (1.02-17.4)**
Kidney failure	1 (3)	17 (3)	0.9	0.8	0.76 (0.08-7.25)
Liver failure	1 (3)	6 (1)	0.4	0.4	2.85 (0.31-26.3)

[a] Concomitant ascending aorta replacement surgery; [b] Transient ischemic attack; [c] Left Ventricular Ejection Fraction < 50%, [d] Acute myocardial infarction.

Table 5
Multivariate logistic regression: Independent predictors of major bleeding.

All prostheses; Bleeding	N = 77 (%)	N = 469 (%)			
	Bleeding	Non-bleeding	P-value, univariate	P-value, multivariate	Odds ratio (95% CI)
Mitral valve	18 (24)	104 (23)	1.0	0.8	1.11 (0.57-2.17)
Age > 75	39 (51)	143 (31)	<0.001	0.06	1.74 (0.97-3.10)
Female	45 (58)	294 (63)	0.5	0.8	0.93 (0.53-1.64)
Asc Ao replacement [a]	69 (90)	394 (84)	0.2	0.6	1.25 (0.54-2.91)
Hypertension	58 (75)	290 (62)	0.02	0.2	1.51 (0.82-2.77)
Diabetes	15 (20)	61 (13)	0.1	0.5	1.26 (0.62-2.56)
Previous Stroke/TIA [b]	12 (16)	54 (12)	0.3	0.9	0.96 (0.45-2.02)
Heart failure [c]	31 (40)	123 (26)	0.01	0.4	1.34 (0.72-2.48)
Previous bleeding	18 (23)	39 (8)	<0.001	0.003	**2.84 (1.43-5.62)**
Previous AMI [d]	20 (26)	63 (13)	0.005	0.1	1.63 (0.86-3.08)
Alcohol overconsumption	4 (5)	7 (2)	0.03	0.07	3.63 (0.91-14.5)
NSAID [e]/Antiplatelet drugs	4 (5)	8 (2)	0.05	0.1	2.74 (0.72-10.4)
Atrial fibrillation	31 (40)	181 (39)	0.8	0.6	0.86 (0.47-1.57)
Vascular disease	5 (7)	13 (3)	0.09	0.8	1.15 (0.34-3.81)
Kidney failure	7 (9)	11 (2)	0.002	0.1	2.62 (0.83-8.29)
Liver failure	2 (3)	5 (1)	0.3	0.5	1.84 (0.30-11.1)

[a] Concomitant ascending aorta replacement surgery, [b] Transient ischemic attack; [c] Left Ventricular Ejection Fraction < 50%, [d] Acute myocardial infarction; [e] Non-steroidal anti-inflammatory drugs.

time. However, each of these 7 patients received this drug following an acute coronary syndrome, making the association with TE misleading. Consequently, this variable is not accounted for in the multivariate analysis for TE.

Discontinuation of Warfarin

A total of 38 patients' warfarin treatment was discontinued for various reasons, mostly due to the advanced stages of cancer, major bleeding, end-stage dementia, multiple falls or a combination of these reasons. All of these patients received low-molecular-weight heparin instead. These patients were all terminally ill, mainly as a result of malignant diseases, when the decision to discontinue warfarin treatment was made. Nineteen of these patients were dead within three months of their warfarin treatment being discontinued.

Mortality

A total of 85 patients in Malmö and Sundsvall died during the 4 years of monitoring. The mortality rate was 4.5 per 100 patient-years (95% CI: 3.6-5.5). The mean age (79.3 ± 10.3 years) of these patients was higher than the mean age of the total cohort (67.9 ± 14.5), p <0.001. Twelve (14%) were valve-related and 42 (49%) cardiac-related. The valve-related deaths were due to two gastrointestinal bleeding, two intracerebral bleeding, two ruptures of aortic aneurysm, one subdural bleeding, one aortic dissection, one chronic iron-deficiency anemia (severe) and three ischemic strokes.

Table 6
Estimated hazard ratios for all causes of death.

Variables	Hazard Ratio	(95% CI)	P-value
Mitral valve	0.87	(0.49-1.54)	0.63
Age	**1.03**	**(1.001–1.05)**	0.038
Hypertension	**2.41**	**(1.28–4.54)**	0.006
Diabetes	**2.38**	**(1.34-4.25)**	0.003
Alcohol overconsumption	**5.23**	**(1.72–15.9)**	0.003
Female	0.81	(0.48-1.36)	0.42
Asc Ao replacement [a]	0.88	(0.26-2.98)	0.84
Previous Stroke/TIA [b]	1.50	(0.87-2.60)	0.14
Heart failure [c]	1.55	(0.91-2.64)	0.11
Previous bleeding	0.91	(0.48-1.75)	0.79
Previous AMI [d]	1.31	(0.73-2.37)	0.37
Atrial fibrillation	0.65	(0.38-1.12)	0.12
Vascular disease	1.47	(0.67-3.19)	0.34

[a] Concomitant ascending aorta replacement surgery, [b] Transient ischemic attack; [c] Left Ventricular Ejection Fraction < 50%, [d] Acute myocardial infarction.

By means of multivariate Cox regression analysis, significant predictors of mortality are presented in Table 6. Valve position was not a significant risk factor. To investigate the mortality further, the standardized mortality/morbidity ratio (SMR) was calculated. A total of 1,359,769 person-years were gathered from Statistics Sweden, an administrative agency of the Swedish government. The different groups were matched on age, gender, region and year. SMR for mortality and AMI are presented in Table 7.

Discussion

The present study demonstrates that patients with MHV managed at a clinical setting with high TTR levels, have a higher incidence of TE and major bleeding than previously reported in observational and randomized clinical trials. TE rates were as high as 1.8 and 2.2 per 100 patient-years in the AVR group and the MVR group, respectively, and major bleeding reaching 4.3 per 100-patient-years. These incidence rates are higher than in other reported trials [9,11,14], probably due to the fact that this cohort is representative of a clinical setting encompassing older patients with more comorbidities, and which has no exclusion criteria. Due to the variability of TE and bleeding incidences from one study to another with the same prostheses, it is therefore obvious that traditional patient-related risk-factors that are included in the various studies are more crucial than the prosthesis itself. At the same time, the recent randomized trials for specific valves may not be representative of the experience in general, with complication rates differing from clinical practice.

Sweden has previously reported a very high level of warfarin treatment quality as measured by TTR, in many cases even better that what has been achieved in prospective randomized clinical trials (RCT) of anticoagulation treatment with warfarin [19]. TTR in our patients with MHV was 91.8% in Malmö for the target range of INR 2.0-4.0 and 76.2% in Sundsvall for the range of INR 2.0-3.0, which is, to our knowledge, the highest TTR levels within these INR ranges ever reported in a population-based setting in patients with MHV. The prospective approach, with the aid of AuriculA, excludes many of the

Table 7
The standard mortality/morbidity ratio (SMR) for mortality and AMI.

	Observed	Expected	SMR	95 % CI
Mortality	85	86.1	0.99	0.8-1.2
Acute myocardial infarction	26	28.7	0.87	0.5-1.2

possible biased conditions related to previous observational studies, which have, presumably, underestimated the complication rates [20]. In the light of these findings there are reports showing that improving the quality of oral anticoagulation reduces the rate of TEs in patients with MHV [21].

Heart failure, vascular disease and previous AMI were independent risk factors for the combined endpoint of TE and AMI, while vascular disease was significant risk factor for TE. Interestingly, the ESC, ACCP and ACC/AHA classify heart failure as a patient-related risk factor in order to raise the target INR range. Previous versions of the guidelines included atherosclerotic vascular disease as a risk factor, however this is absent from the latest guidelines. The guidelines also emphasize atrial fibrillation as a risk factor for TE, and suggest raising the INR target range or adding aspirin. However, our results did not even show trends towards a correlation between atrial fibrillation and TE. This could be due to a better INR control in our patients compared to those in earlier studies [22,23].

Incidence rates of major bleeding demonstrate a wide range in different cohort studies, and a recent systematic review reported an incidence of major bleeding of approximately 2 per 100 patient-years in RCTs and observational studies [24]. The incidence of major bleeding events in our study was at the higher end of the range of the published data. This might be explained by the clinical population with considerable comorbidities (including patients with cancer) which are usually excluded in RCTs. Some studies have compared low-intensity with high-intensity oral anticoagulation, demonstrating a decrease in bleeding events without an increase in embolic events [25,26]. The higher INR target range of 2.0-4.0 for Malmö might partially account for the higher incidence rate of bleeding in the Malmö cohort, despite that the achieved mean INR was very similar to the cohort in Sundsvall. In addition, the Malmö cohort was significantly older and burdened with more comorbidities.

In accordance with previous studies dealing with atrial fibrillation [19,27], there was an obvious correlation with previous major bleeding and age, where previous major bleeding independently predicted major bleeding events and age > 75 had a clear tendency to significance. Concomitant therapy with warfarin and aspirin is rare in Sweden. All those patients who received aspirin and/or clopidogrel had suffered an acute coronary syndrome, and were treated for a limited time. Consequently, we do not have a sufficient number of cases to evaluate this therapy. The guidelines recommend the addition of aspirin for all patients with MHV (evidence B) which would likely increase the risk of bleeding further in this cohort.

The standardized mortality ratio of 0.99 indicates a mortality rate equal to that of the general population. This is in a way remarkable, in particular as the incidences of TE and major bleeding are comparatively high in our cohort. Weber et. al [8] demonstrated that in patients younger than 60 years old, biologic aortic valve replacement was associated with reduced mid-term survival compared with a propensity matched cohort of patients with MHV, and patients with bioprosthetic valves receiving oral anticoagulation due to atrial fibrillation presented with 100% late survival. The large analysis of 41,227 patients after aortic valve surgery from the society for Cardiothoracic Surgery of Great Britain and Ireland national database [28] demonstrated similar advantages for MHV, the hazard ratio for improved survival was 1.46 (95% CI; 1.35-1.57) if the patient had implanted a MHV. Other studies have reported similar outcome [15,29]. These results may suggest a potential protective effect of warfarin on mortality in any valve type. However, due to retrospective character of these studies, there could be patients characteristics not included in the multivariate models that could have confounded the results. Also degenerative influence (usually after 10-15 years) could be a contributing factor. Even though our results alongside aforementioned studies may indicate a protective effect of warfarin, it is complex to indicate a causality. Nevertheless, the mortality rate in our cohort with tight anticoagulation control seems not outweigh that of the general population.

Limitations

We are aware of the limitations of this study. The monitoring does not cover the entire post cardiac surgery period for every patient and thus different exposure times exist for each patient. Although the risk of TE and major bleeding exhibit a higher hazard the first months after valve insertion due to insufficient endothelialisation, it is subsequently assumed that the risk is linearized and constant over time. Since the majority of the cohort received their valve replacements before the study period, this would in fact lower the adverse incidences which is not the case for our cohort. Even though outcomes were registered prospectively, many of the baseline data were gathered retrospectively, which cannot entirely exclude bias. Furthermore, the models of the valves are not considered in this unselected clinical population, which makes an assessment of the different valve types difficult. However, most of the valve replacements were conducted in the 1990s and subsequently (median: 2001), which may imply that the majority of the patients received the bileaflet valve.

Conclusion

In summary, this population-based study, which included all patients with MHV at two anticoagulation centres, indicates that there is a considerably higher incidence of TE and major bleeding events than indicated by previous reports. This analysis confirms the predictive value of previously identified risk factors for thrombosis and mortality. However atrial fibrillation was not associated to TE. Furthermore, it appears that the mortality and AMI rate is equal to that of the general population.

Conflict of Interest

None declared.

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References

[1] Butchart EG, Li HH, Payne N, Buchan K, Grunkemeier GL. Twenty years' experience with the Medtronic Hall valve. J Thorac Cardiovasc Surg 2001;121:1090–100.
[2] Butchart EG, Ionescu A, Payne N, Giddings J, Grunkemeier GL, Fraser AG. A new scoring system to determine thromboembolic risk after heart valve replacement. Circulation 2003;108(Suppl. 1):II68–74.
[3] Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). European journal of cardio-thoracic surgery: official journal of the European Association for Cardio-thoracic Surgery 2012;42:S1–44.
[4] Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic therapy and prevention of thrombosis, 9th ed: american college of chest physicians evidence-based clinical practice guidelines. Chest J 2012;141:e576S–600S.
[5] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;2014.
[6] Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al. Dabigatran versus Warfarin in Patients with Mechanical Heart Valves. N Engl J Med 2013;369:1206–14.
[7] Brennan JM, Edwards FH, Zhao Y, O'Brien S, Booth ME, Dokholyan RS, et al. Long-Term Safety and Effectiveness of Mechanical Versus Biologic Aortic Valve Prostheses in Older Patients: Results From the Society of Thoracic Surgeons Adult Cardiac Surgery National Database. Circulation 2013;127:1647–55.
[8] Weber A, Noureddine H, Englberger L, Dick F, Gahl B, Aymard T, et al. Ten-year comparison of pericardial tissue valves versus mechanical prostheses for aortic valve replacement in patients younger than 60 years of age. J Thorac Cardiovasc Surg 2012;144:1075–83.

[9] Koertke H, Zittermann A, Tenderich G, Wagner O, El-Arousy M, Krian A, et al. Low-dose oral anticoagulation in patients with mechanical heart valve prostheses: final report from the early self-management anticoagulation trial II. Eur Heart J 2007;28:2479–84.
[10] Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. J Am Coll Cardiol 2000;36:1152–8.
[11] Hering D, Piper C, Bergemann R, Hillenbach C, Dahm M, Huth C, et al. Thromboembolic and bleeding complications following St. Jude Medical valve replacement: results of the German Experience With Low-Intensity Anticoagulation Study. Chest 2005;127:53–9.
[12] Akhtar RP, Abid AR, Zafar H, Khan JS. Aniticoagulation in patients following prosthetic heart valve replacement. Ann Thorac Cardiovasc Surg Off J Assoc Thorac Cardiovasc Surg Asia 2009;15:10–7.
[13] Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg 2008;135:732–8.
[14] Stassano P, Di Tommaso L, Monaco M, Iorio F, Pepino P, Spampinato N, et al. Aortic valve replacement: a prospective randomized evaluation of mechanical versus biological valves in patients ages 55 to 70 years. J Am Coll Cardiol 2009;54:1862–8.
[15] Brown ML, Schaff HV, Lahr BD, Mullany CJ, Sundt TM, Dearani JA, et al. Aortic valve replacement in patients aged 50 to 70 years: improved outcome with mechanical versus biologic prostheses. J Thorac Cardiovasc Surg 2008;135:878–84 [discussion 84].
[16] Grzymala-Lubanski B, Själander S, Renlund H, Svensson PJ, Själander A. Computer aided warfarin dosing in the Swedish national quality registry AuriculA – Algorithmic suggestions are performing better than manually changed doses. Thromb Res 2013;131:130–4.
[17] Schulman S, Kearon C, the SOCOAOTS, Standardization Committee Of The International Society On T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692–4.
[18] Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993;69:236–9.
[19] Wieloch M, Sjalander A, Frykman V, Rosenqvist M, Eriksson N, Svensson PJ. Anticoagulation control in Sweden: reports of time in therapeutic range, major bleeding, and thrombo-embolic complications from the national quality registry AuriculA. Eur Heart J 2011;32:2282–9.
[20] Bodnar E, Horstkotte D. Potential flaws in the assessment of minor cerebrovascular events after heart valve replacement. J Heart Valve Dis 1993;2:287–90.
[21] Koertke H, Minami K, Bairaktaris A, Wagner O, Koerfer R. INR self-management following mechanical heart valve replacement. J Thromb Thrombolysis 2000; 9(Suppl. 1):S41–5.
[22] Turpie A, Gent M, Laupacis A, Latour Y, Gunstensen J, Basile F, et al. A Comparison of Aspirin with Placebo in Patients Treated with Warfarin after Heart-Valve Replacement. N Engl J Med 1993;329:524–9.
[23] Le Tourneau T, Lim V, Inamo J, Miller FA, Mahoney DW, Schaff HV, et al. Achieved anticoagulation vs prosthesis selection for mitral mechanical valve replacement: a population-based outcome study. Chest 2009;136:1503–13.
[24] Roskell NS, Samuel M, Noack H, Monz BU. Major bleeding in patients with atrial fibrillation receiving vitamin K antagonists: a systematic review of randomized and observational studies. Europace Eur Pacing Arrhythmias Card Electrophysiol J Work Groups Card Pacing Arrhythmias Card Cell Electrophysiol Eur Soc Cardiol 2013;15:787–97.
[25] Saour JN, Sieck JO, Mamo LAR, Gallus AS. Trial of Different Intensities of Anticoagulation in Patients with Prosthetic Heart Valves. N Engl J Med 1990;322: 428–32.
[26] Acar J, Iung B, Boissel JP, Samama MM, Michel PL, Teppe JP, et al. AREVA: multicenter randomized comparison of low-dose versus standard-dose anticoagulation in patients with mechanical prosthetic heart valves. Circulation 1996;94:2107–12.
[27] Sjalander A, Engstrom G, Berntorp E, Svensson P. Risk of haemorrhagic stroke in patients with oral anticoagulation compared with the general population. J Intern Med 2003;254:434–8.
[28] Dunning J, Gao H, Chambers J, Moat N, Murphy G, Pagano D, et al. Aortic valve surgery: marked increases in volume and significant decreases in mechanical valve use–an analysis of 41,227 patients over 5 years from the Society for Cardiothoracic Surgery in Great Britain and Ireland National database. J Thorac Cardiovasc Surg 2011;142:776–82 [e3].
[29] Jamieson WRE, Ye J, Higgins J, Cheung A, Fradet GJ, Skarsgard P, et al. Effect of Prosthesis-Patient Mismatch on Long-Term Survival With Aortic Valve Replacement: Assessment to 15 Years. Ann Thorac Surg 2010;89:51–9.

Paper II

Cardiorenal

Glomerular filtration rate and association to stroke, major bleeding, and death in patients with mechanical heart valve prosthesis

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Aims The impact of estimated glomerular filtration rate (eGFR) on adverse events in patients with mechanical heart valves (MHVs) is unknown. We analyzed the independent association of eGFR and thromboembolism (TE), major bleeding, and mortality in patients with MHV in an observational cohort study.

Methods and results All patients (n = 520) with MHV replacement on anticoagulation treatment were followed up prospectively regarding TE, major bleeding, and death at 2 anticoagulation centers during 2008 to 2011. The mean age was 69 years, 72% with aortic valve replacement, and time in therapeutic range 2.0 to 4.0 was 91%. The incidence of the combined end point of major bleeding, TE, and death increased sharply with each decreasing eGFR stratum: 5.5, 8.4, 16, and 32 per 100 patient-years for eGFR >60, 45 to 60, 30 to 45, and <30 mL/min per 1.73 m^2, respectively. After multivariate adjustment for comorbidities, every unit decrease in eGFR increased the risk of major bleeding by 2%, death by 3%, and the combined end point by 1%. There was no association between eGFR and TE. There was an increased proportion of international normalized ratio >3.0 and >4.0 and decreasing time in therapeutic range for each decreasing eGFR stratum ($P < .001$ for trend). The hazard ratios of the combined end point for eGFR <30, 30 to 45, and 45 to 60 mL/min per 1.73 m^2 were 3.2 (95% CI 1.8-5.6), 1.5 (95% CI 0.9-2.5), and 0.9 (95% CI 0.6-1.5), respectively, compared to eGFR >60 mL/min per 1.73 m^2.

Conclusion In patients with MHV on anticoagulation, eGFR is an independent predictor of major bleeding and death and not TE. (Am Heart J 2015;170:559-65.)

Despite the reported benefit of warfarin in prevention of thrombotic events in patient with mechanical heart valves (MHVs), adverse events are not uncommon as demonstrated in a recent cohort, with an incidence of 1.8% and 4.3% per year for thromboembolism (TE) and major bleeding, respectively.[1] Current guidelines do not consider chronic kidney disease (CKD) as a risk factor for adverse events when choosing an optimum target international normalized ratio (INR) or when improving the quality of anticoagulation treatment given to these patients. Moreover, CKD is increasing due to the aging population and will be more frequently a common comorbidity among patients with MHV.

In patients with atrial fibrillation, a moderate impairment of the kidney function with an estimated glomerular filtration rate (eGFR) of 30 to 59 mL/min per 1.73 m^2 appears as an independent predictor of stroke (hazard ratio approximately 1.5).[2-4] Adjusted dose warfarin markedly reduces the stroke risk.[4] Even at high time in therapeutic range (TTR) settings, impaired renal function is associated with high incidence of bleeding events in patient with atrial fibrillation,[5] whereas a recent large observational study showed that patients with atrial fibrillation and moderate, severe, and end-stage CKDs on warfarin treatment were associated with a lower risk of the composite end point of death, myocardial infarction, and ischemic stroke without a higher risk of bleeding than patients without warfarin treatment.[6] The choice between a mechanical and biological valve is mainly determined not only by the age but also by estimating the risk of warfarin-associated complications such as bleeding and TE with an MHV as compared to the risk of structural valve deterioration in bioprosthetic valves. Despite that structural valve deterioration is accelerated in patients with CKD, the European guidelines favor the choice of bioprosthesis due to the risk of complications with MHV and the poor

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long-term survival irrespective of valve type.[7] To our knowledge, the association between different stages of eGFR and warfarin-associated complications and mortality in patients with MHV has not previously been investigated.

The objective of the present analysis was to investigate the incidences of stroke/systemic embolism (SE), major bleeding events, and mortality in association to eGFR in patients with MHV.

Methods

The design and circumstances of the population-based cohort in Malmö and Sundsvall have been described in detail elsewhere.[1,8] Briefly, all patients with MHV on anticoagulation treatment at these centers between January 1, 2008, and December 21, 2011, were prospectively followed up and monitored in the Swedish national quality registry for atrial fibrillation and anticoagulation, AuriculA. All outpatients who are treated with warfarin at these centers are referred to regional anticoagulation clinics to have their treatment monitored regularly in AuriculA. The primary end points, TE and major bleeding, were recorded prospectively. A review of events was performed by one of the authors to ensure that complications were correctly classified. The registry includes a Web-based dosing program and decision support that uses an algorithm to calculate warfarin dosage based on the last 2 or 3 INR results.[9] During the study period, there were different target INR ranges for patients with MHVs in Malmö and Sundsvall due to local traditions. The target INR range was 2.0 to 4.0 for all the MHVs in Malmö, whereas patients in Sundsvall had 2.0 to 3.0 for aortic valve replacement (AVR) and 2.5 to 3.5 for mitral valve replacement (MVR), irrespective of patient-related risk factors.

The measurement of the kidney function was obtained from all laboratory results from the regions during the study period. Age, gender, and the mean of plasma creatinine were used to estimate the eGFR, which was calculated according to the revised Lund-Malmö equation, derived and internally validated at the present university hospital.[10] This equation performed better than the 4-variable Modification of Diet in Renal Disease (MDRD) study equation and the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation across glomerular filtration rate, age, and body mass index in a large Swedish cohort.[11]

Thromboembolism was defined according to the guidelines for reporting mortality and morbidity after cardiac valve intervention.[12] Major bleeding events were defined according to The International Society on Thrombosis and Haemostasis definitions.[13] Thromboembolism, major bleeding, and death were used as a combined end point for some of the analysis. Time in therapeutic range was calculated according to the Rosendaal algorithm with linear interpolation.[14] The primary material consisted of 546 patients, but due to insufficient data on plasma creatinine in 26 patients (4.7%), the analysis was made on 520 patients. The study was approved by the regional ethical review board in Lund.

Statistics

Skewness was calculated for continuous data to assess normal distribution. Patient characteristics were compared between groups using a χ^2 test for categorical variables and *t* test or Mann-Whitney *U* test for continuous measures, as appropriate. Frequency and percentages were calculated for categorical variables. Patient characteristics are presented in prespecified subgroups defined by eGFR strata (<30, 30-45, 45-60, and >60) according to the international classification of CKD. Univariate analysis was performed, and statistically significant covariates were included in the multivariate analysis. In model 1, unadjusted and adjusted hazards of eGFR as a continuous variable were estimated by Cox regression models to confirm association to TE, major bleeding, and death and as a combined end point. In model 2, univariate and multivariate analyses were performed for the combined end point according to the aforementioned eGFR strata with eGFR >60 as the reference. The incidence of the adverse events was calculated using the person-time module in OpenEpi, version 3.03 (www.openepi.com). All tests were performed 2 tailed, and $P < .05$ was considered significant. All analyses were performed using SPSS statistics (version 22.0; SPSS, Inc, IBM Corporation, Armonk, NY).

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Results

Patient characteristics

A total of 520 patients (62% male) with an accrued total of 1,813 patient-years were included in the analysis. There were 397 patients (76.3%) with an INR target range of 2.0 to 4.0 for all types of MHV and 123 patients (23.7%) with an INR target range of 2.0 to 3.0 for AVR and 2.5 to 3.5 for MVR. The adjusted mean TTR for INR of 2.0 to 4.0 was 90.1%, and for INR of 2.0 to 3.0, 77.1%. A total of 30,192 INR samples were gathered in the cohort. The achieved mean (SD) INR in the INR target range of 2.0 to 4.0 was 2.86 (±0.89) and 2.89 (±0.92) for AVR and MVR, respectively, and in the INR target range of 2.0 to 3.0, 2.60 (±0.63) and 2.72 (±0.86) for AVR and MVR, respectively. Baseline patient characteristics within the different eGFR strata are presented in Table I. Risk factors such as hypertension, diabetes, atrial fibrillation, heart failure, and previous stroke and bleeding events were all more common with decreasing eGFR strata ($P < .001$ for

Table I. Patient characteristics stratified according to eGFR

	eGFR strata, mL/min per 1.73 m^2				
n (%)	All	>60	45-60	30-45	<30
n	520	330	96	61	33
Age (y)	69 (±14)	62 (±12)	76 (±12)	83 (±9)	83 (±9)
Male	320 (62)	219 (66)	56 (58)	30 (49)	15 (46)
AVR	376 (72)	250 (76)	61 (64)	44 (72)	21 (64)
MVR	118 (23)	63 (19)	32 (33)	14 (23)	9 (27)
AVR/MVR	26 (5)	17 (5)	3 (3)	3 (5)	3 (9)
Hypertension	332 (64)	188 (57)	73 (76)	44 (72)	27 (82)
Diabetes	76 (15)	37 (11)	15 (16)	14 (23)	10 (30)
Previous stroke	65 (13)	23 (7)	17 (18)	16 (26)	9 (27)
Previous bleeding	56 (11)	19 (6)	16 (17)	12 (20)	9 (27)
Vascular disease	18 (3)	5 (2)	7 (7)	2 (3)	4 (12)
Antiplatelet agent	12 (2)	6 (2)	5 (5)	1 (2)	0
Atrial fibrillation	204 (39)	105 (32)	48 (50)	32 (53)	19 (58)
Heart failure	150 (29)	71 (22)	30 (31)	28 (46)	21 (64)
LVEF 35%-50%	128 (25)	61 (19)	25 (26)	24 (39)	18 (55)
LVEF <35%	22 (4)	10 (3)	5 (5)	4 (7)	3 (9)
eGFR	63.9 (±20.3)	76.3 (±11.8)	52.7 (±4.3)	38.0 (±4.6)	20.9 (±5.5)
CHA_2DS_2-VASc	2.93 (±1.52)	2.40 (±1.36)	3.5 (±1.35)	4.02 (±1.36)	4.45 (±1.0)
HAS-BLED	1.30 (±0.85)	1.03 (±0.72)	1.53 (±0.79)	1.79 (±0.82)	2.39 (±0.83)
INR	2.80	2.76	2.84	2.89	2.88
TTR 2.0-3.0	65.6	67.5	65.0	60.3	58.1
TTR 2.0-4.0	90.7	91.4	91.3	88.8	87.2
% of INR >4.0	7.3	6.2	8.0	9.5	11.6
% of INR >3.0	34	36.8	37.8	39	34

Values are expressed as n (%) or means ± SD. Abbreviation: *LVEF*, left ventricular ejection fraction.

linear association). The proportion of INR <2.0 and mean INR were similar between the kidney stages, whereas there was an increased proportion of INR >3.0 and >4.0; congestive heart failure, hypertension, age ≥75, diabetes mellitus, stroke/transient ischemic attack/TE, vascular disease, age 65-74, female sex (CHA_2DS_2-VASc); and hypertension, abnormal liver and renal function, stroke, bleeding, labile INRs (HAS-BLED) value and decreasing TTR 2.0 to 3.0 for each decreasing eGFR stratum ($P < .001$ for linear association).

Events and effect of eGFR

Unadjusted hazards of eGFR as a continuous variable were estimated for the primary end points including the combined end point in Table II. Major bleeding, death, and the combined end point were all significant in the univariate, whereas no association to TE was found. After multivariate adjustment for comorbidities, every unit decrease in eGFR increased the risk of major bleeding by 2%, death by 3%, and the combined end point by 1%.

In total, there were 75 major bleeding events, 33 stroke/SE, and 81 deaths in the cohort. The annual major bleeding and death rate increased sharply as the eGFR declined. The major bleeding rate for patients with eGFR >60, 60 to 45, 45 to 30, and <30 mL/min per 1.73 m^2 was 3.0%, 5.4%, 6.2%, and 16.7%, respectively ($P < .001$ for trend) and 1.8%, 4.6%, 10.0%, and 28.8%, respectively ($P < .001$ for trend) for the annual mortality rate. The annual risk of stroke/SE for patients with eGFR >60, 60 to 45, 45 to 30, and <30 mL/min per 1.73 m^2 was 1.7%, 1.5%, 3.9%, and 1.2%, respectively. A similar association was observed when estimating glomerular filtration rate with CKD-EPI and MDRD for all outcomes.

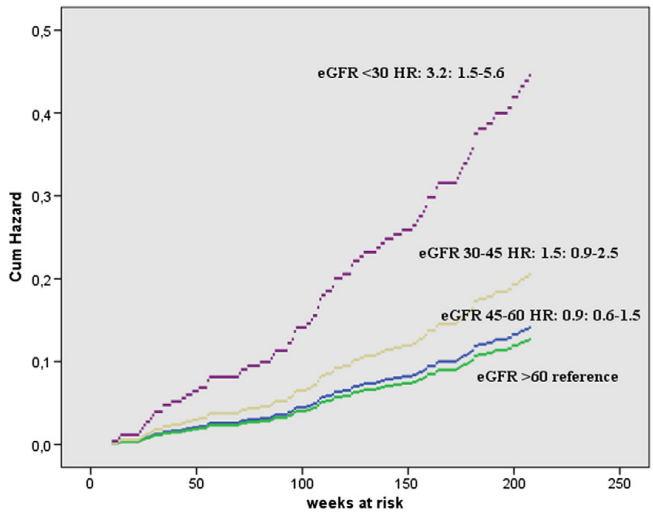
Table II. Unadjusted and adjusted hazards of eGFR on outcomes and combined end point

Univariate	HR	95% CI	*P*
TE	1.00	0.98-1.02	.75
Major bleeding	0.97	0.96-0.98	<.001
Death	0.95	0.94-0.96	<.001
Combined end point	0.97	0.96-0.98	<.001
Multivariate			
Major bleeding*	0.98	0.96-0.99	.005
Death†	0.97	0.96-0.99	<.001
Combined end point‡	0.99	0.97-0.997	.014

Abbreviation: *HR*, hazard ratio.
* Adjusted for age, previous major bleeding event, and concomitant antiplatelet treatment.
† Adjusted for age, hypertension, diabetes, previous stroke, heart failure (left ventricular ejection fraction <50%), atrial fibrillation, concomitant antiplatelet treatment, and time since valve replacement.
‡ Adjusted for age, hypertension, diabetes, previous stroke, heart failure (left ventricular ejection fraction <50%), atrial fibrillation, previous major bleeding event, concomitant antiplatelet treatment, and time since valve replacement.

The cumulative hazard of the combined end point adjusted for confounders is analyzed with eGFR >60 as the reference in Figure. The incidence rate for the combined end point across eGFR strata with crude and

Figure



Cumulative hazard ratio of the combined end point death, major bleeding, and stroke/SE stratified by eGFR. *Adjusted for age, hypertension, diabetes, heart failure, concomitant antiplatelet agent, and time since valve replacement.

adjusted risks is reported in Table III. The adjusted risk of the combined end point increased as the eGFR decreased, with an increase of 320% with an eGFR <30 mL/min per 1.73 m^2 compared to the reference, eGFR >60 mL/min per 1.73 m^2.

Patients with major bleeding and death had a significantly lower eGFR than patients without bleeding and survivors, respectively ($P < .001$), and were older ($P < .001$) and had an increased percentage of time with INR >4.0 ($P = .006$ and $P < .001$, respectively) (Table IV). There was a consistent difference in eGFR estimated by all 3 equations between patients with major bleeding compared to patients without an event. Differences in mean eGFR for major bleeding were consistent in all the equations, revised Lund-Malmö equation (11.2 mL/min per 1.73 m^2), CKD-EPI (12.2 mL/min per 1.73 m^2), and MDRD (10.5 mL/min per 1.73 m^2). Patients with major bleeding and death had a significantly higher proportion of eGFR <30, <45, and <60 mL/min per 1.73 m^2 compared to patients without bleeding and survivors, respectively. Among the patient with TE and non-TE, no difference was seen in eGFR, eGFR cut-offs, mean age, or TTR.

Table III. Incidence of the combined end point in relation to eGFR strata and unadjusted and adjusted hazards with eGFR >60 as reference

	eGFR strata, mL/min per 1.73 m^2			
Combined end point	>60*	45-60	30-45	<30
n	65	29	30	27
Incidence†	5.5 (4.2-6.9)	8.4 (5.7-11.9)	15.8 (10.9-22.3)	31.8 (21.4-45.6)
HR, crude	1.0	1.6 (1.0-2.4)	3.1 (2.0-4.8)	7.4 (4.7-11.6)
HR, adjusted‡	1.0	0.9 (0.6-1.5)	1.5 (0.9-2.5)	3.2 (1.8-5.6)

Values are expressed as hazard ratio (95% CI).
* Reference group.
† Incidence (95% CI) per 100 patient-years.
‡ Adjusted for age, hypertension, diabetes mellitus, heart failure, concomitant antiplatelet agent, and time since valve replacement.

Discussion

The main findings of the present study were as follows: First, the incidence of the combined end point, major bleeding events, and death increased as the eGFR decreased. Second, there was an independent association of events with eGFR such that every unit decrease in eGFR increased the risk of major bleeding by 2%, death by 3%, and the combined end point by 1%, whereas no association between eGFR and stroke/SE was found. Third, the adjusted risk of the combined end point was more than 3 times higher for eGFR <30 mL/min per 1.73 m^2 compared to eGFR >60 mL/min per 1.73 m^2. Fourth, the proportion of patients with deranged INR values increased as the eGFR decreased.

The prognostic and predictive ability of eGFR on mortality and cardiovascular events has been proven not only in high-risk patients with atrial fibrillation[2,6,15-17] but

Table IV. Characteristics of patients with major bleeding and stroke/SE; proportion of different eGFR strata, out-of-range INR values, TTR, and mean eGFR by the different equations

	No bleeding	Bleeding	No stroke/SE	Stroke/SE	No death	Death
No. of patient	445	75	487	33	461	81
Age (y)	67.5 (±14)	74.1 (±12)*	68.4 (±14)	69.6 (±13)	66.4 (±14)	79.8 (±10)*
TTR 2.0-3.0‡	66.4	61.1†	65.7	64.6	66.6	60.1*
TTR 2.0-4.0§	91.3	87.8†	90.8	89.5	91.4	87.7†
% of INR >4.0	7.0 (±6.9)	9.1 (±7.4)†	7.2 (±7.0)	8.4 (±7.2)	6.4 (±6.1)	11.8 (±9.3)*
% of INR >3.0	33.7 (±16.0)	35.3 (±14.3)	33.9 (±15.8)	34.6 (±14.7)	33.1 (±15.3)	38.7 (±15.5)†
% of INR <2.0	14.3 (±14.3)	17.9 (±12.8)†	14.9 (±14.4)	12.9 (±7.5)	14.6 (±14.1)	15.8 (±14.2)
eGFR, LM rev	65.6 (±20)	54.4 (±22)*	64.0 (±20)	63.9 (±21)	67.5 (±18)	44.8 (±22)*
eGFR, CKD-EPI	73.3 (±22)	61.1 (±25)*	71.7 (±23)	71.6 (±24)	75.5 (±21)	50.4 (±24)*
eGFR, MDRD	72.2 (±23)	61.7 (±25)*	70.6 (±23)	72.0 (±25)	73.9 (±21)	52.9 (±27)*
eGFR <30, % (n)‖	5.2 (23)	17.3 (13)*	7.2 (35)	3.0 (1)	2.3 (10)	32 (26)*
eGFR <45, % (n)‖	16.6 (74)	33.3 (25)*	18.7 (91)	24.2 (8)	12.3 (54)	55.6 (45)*
eGFR <60, % (n)‖	36 (160)	56 (33)*	38.8 (189)	39.4 (13)	32.1 (141)	75.3 (61)*
HAS-BLED	1.23 (±0.8)	1.68 (±1.0)*	1.30 (±0.9)	1.24 (±0.8)	1.16 (±0.8)	1.88 (±0.9)*
CHA_2DS_2-VASc	2.85 (±1.5)	3.40 (±1.5)†	2.93 (±1.5)	2.88 (±1.5)	2.69 (±1.5)	4.06 (±1.2)*

Values are expressed as % (n) or means ± SD. Abbreviation: *LM rev*, revised Lund-Malmö equation.
* $P < .001$.
† $P < .05$.
‡ Analyzed for INR target ranges 2.0 to 3.0, 2.5 to 3.5, and 2.0 to 4.0.
§ Only INR target range 2.0 to 4.0.
‖ Estimated by the revised Lund-Malmö equation, mL/min/1.73 m^2.

also in the general population.[18] Thus, one would expect poorer outcomes in patients with CKD and concomitant risk factors in patients with MHV. In patients with atrial fibrillation, CKD is common with conflicting evidence regarding the use of warfarin in patients with severe CKD requiring hemodialysis,[19] whereas recent reports have showed that warfarin reduces the risk of stroke and TE among patients with moderate and severe CKDs.[6,16] Increasing age, hypertension, diabetes, and heart failure are increasingly common among patients with CKD, and in addition, it may even be a marker for end-organ damage from hypertension and diabetes. As a result, it is notable that eGFR as a continuous variable adjusted for significant predictors, independently predicted major bleeding events. The added predictive ability of eGFR in this context could be attributable to the fact that the other clinical risk factors do not account for the duration, severity, or treatment status of the different variables.

The risk of bleeding among patients with CKD is not consistent in these cohorts, probably due to differences in warfarin control and standard care between the centers and countries. The risk of bleeding in warfarin-treated patients seems to be higher in patients with CKD than patients with normal renal function.[17,20] The altered physiologic mechanisms leading to the influence in hemostasis in patients with CKD paradoxically increase the risk of thrombosis and bleeding simultaneously.[21] However, the increased risk of bleeding with worsening kidney function may also in part be attributable to poorer anticoagulation control due to altered warfarin dosage in patients with CKD.[22] Supratherapeutic INR values, such as INR >4.0 and INR >3.0, were more common with each decreasing eGFR stratum as well as decreasing TTR of 2.0 to 3.0. This suggests that INR values out of range in a setting of high TTR in patients with CKD substantially contribute to the increased risk of major bleeding events in patients with MHV and implicate that these patients have a greater need of warfarin dose adjustment to reduce supratherapeutic INR values and to increase the TTR. These results are consistent with another Swedish study in a setting of high TTR where supratherapeutic INR values were correlated with bleeding events[5] and with the recent study by Friberg et al,[17] which indicated that patients with renal failure and atrial fibrillation with TTR >70% had fewer strokes and particularly fewer bleeding events than patients with lower TTR. The importance of a well-managed anticoagulation control is confirmed in the study by Sjogren et al[23] where patients with heart valve disease had comparatively low incidences of bleeding and TE events. Although the TTR was analyzed within the target range of 2.0 to 4.0 in our cohort, one should interpret the bleeding events in our cohort based on a tight anticoagulation control, which, in case of poor TTR, might have increased the bleeding events even further. There was no difference in the anticoagulation control between the patients with stroke and those without an event.

Remarkably, no association between eGFR and TE could be established, in spite the documented predicting effect of eGFR on TE in patients with atrial fibrillation and anticoagulation treatment.[2,16,24] However, the recently large observational study on atrial fibrillation with different CKD stages[6] showed no difference in the incidence of ischemic stroke for the different kidney stages in different centers in Sweden, as in our cohort. The predicting effect of low eGFR may be leveled out when appropriately anticoagulated (high TTR), due to the markedly decreased risk of stroke with warfarin treatment, which was observed

through patient strata with moderate, severe, and even end-stage CKDs. This finding seems to apply to patients with MHV, which is reassuring because all patients with MHV irrespective of kidney function have an obvious and strong indication for warfarin treatment. In addition, there were no trends toward an association between atrial fibrillation and stroke, which strengthens this argument.

Although publications regarding eGFR of 15 to 60 mL/min per 1.73 m^2 in patients with MHV are absent, there are some retrospective studies investigating dialysis patients undergoing heart valve replacement surgery. There has been much controversy regarding prosthesis valve selection in patients with end-stage renal disease (ESRD) requiring dialysis, due to the accelerated calcification and structural valve deterioration of heart valves in patients with ESRD and the increased risk of complications in patients with MHV and warfarin treatment. One large retrospective study based on long-term clinical results from diagnosis codes of dialysis patients demonstrated no significant difference in survival after valve replacement with bioprostheses versus MHV.[25] This study, in particular, and the poor life expectancy by the nature of their illness have changed the recommendations in the practice guidelines toward selecting bioprostheses in patients with ESRD. However, the observational character in this and previous smaller reported studies,[26,27] may have been associated with a risk of selection bias when choosing the type of valve prosthesis. Moreover, because of the longer life expectancy in dialysis patients today,[28] the potential risk of early calcification of the bioprosthetic valves should be taken into account. This would certainly involve patients with eGFR of 15 to 60 mL/min per 1.73 m^2 not requiring dialysis given the longer life expectancy.

Our study is limited by its observational cohort design and with different INR target ranges between the centers. Although the widened INR target range of 2.0 to 4.0 contributes to higher variability of the INR and higher proportions of supratherapeutic INR values, the obtained mean INR was similar between the centers. Although outcomes were registered prospectively and we were able to account for the most important confounders, residual confounding may still exist. Furthermore, a small proportion of subjects did not have known kidney function (4.7%) during the study period, and some patients had too few INR samples to calculate TTR. The proportion of patients with reduced eGFR, <30 and 30 to 45 mL/min per 1.73 m^2, was too low to establish a careful correlation, and larger studies in patients with MHV are required to reproduce our findings.

Conclusion

In conclusion, in our study consisting of all patients with MHV at 2 anticoagulation centers in a setting of tight anticoagulation control, we found an independent association of decreasing eGFR and major bleeding and death, whereas there was no association with stroke or SE. An eGFR <30 mL/min per 1.73 m^2 was independently associated with more than a 3-fold increase in the combined end point compared to eGFR >60 mL/min per 1.73 m^2. In addition, anticoagulation control was inferior with decreasing eGFR stratum, which might suggest a close monitoring of the INR in patients with impaired renal function and MHV.

References

1. Labaf A, Grzymala-Lubanski B, Stagmo M, et al. Thromboembolism, major bleeding and mortality in patients with mechanical heart valves—a population-based cohort study. Thromb Res 2014;134(2): 354-9.
2. Nakagawa K, Hirai T, Takashima S, et al. Chronic kidney disease and CHADS(2) score independently predict cardiovascular events and mortality in patients with nonvalvular atrial fibrillation. Am J Cardiol 2011;107(6):912-6.
3. Eikelboom JW, Connolly SJ, Gao P, et al. Stroke risk and efficacy of apixaban in atrial fibrillation patients with moderate chronic kidney disease. J Stroke Cerebrovasc Dis 2012;21(6):429-35.
4. Hart RG, Pearce LA, Asinger RW, et al. Warfarin in atrial fibrillation patients with moderate chronic kidney disease. Clin J Am Soc Nephrol 2011;6(11):2599-604.
5. Wieloch M, Jonsson KM, Sjalander A, et al. Estimated glomerular filtration rate is associated with major bleeding complications but not thromboembolic events, in anticoagulated patients taking warfarin. Thromb Res 2013;131(6):481-6.
6. Carrero JJ, Evans M, Szummer K, et al. Warfarin, kidney dysfunction, and outcomes following acute myocardial infarction in patients with atrial fibrillation. JAMA 2014;311(9):919-28.
7. Taylor J. ESC/EACTS Guidelines on the management of valvular heart disease. Eur Heart J 2012;33(19):2371-2.
8. Grzymala-Lubanski B, Labaf A, Englund E, et al. Mechanical heart valve prosthesis and warfarin—treatment quality and prognosis. Thromb Res 2014;133(5):795-8.
9. Grzymala-Lubanski B, Själander S, Renlund H, et al. Computer aided warfarin dosing in the Swedish national quality registry AuriculA—algorithmic suggestions are performing better than manually changed doses. Thromb Res 2013;131(2):130-4.
10. Bjork J, Grubb A, Sterner G, et al. Revised equations for estimating glomerular filtration rate based on the Lund-Malmo Study cohort. Scand J Clin Lab Invest 2011;71(3):232-9.
11. Nyman U, Grubb A, Larsson A, et al. The revised Lund-Malmo GFR estimating equation outperforms MDRD and CKD-EPI across GFR, age and BMI intervals in a large Swedish population. Clin Chem Lab Med 2014;52(6):815-24.
12. Akins CW, Miller DC, Turina MI, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg 2008;135(4):732-8.
13. Schulman S, Kearon C, the SOCOAOTS, Standardization Committee Of The International Society On T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3(4):692-4.
14. Rosendaal FR, Cannegieter SC, van der Meer FJ, et al. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993;69(3):236-9.
15. Apostolakis S, Guo Y, Lane DA, et al. Renal function and outcomes in anticoagulated patients with non-valvular atrial fibrillation: the AMADEUS trial. Eur Heart J 2013;34(46):3572-9.

16. Olesen JB, Lip GY, Kamper AL, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med 2012;367(7): 625-35.
17. Friberg L, Benson L, Lip GY. Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study. Eur Heart J 2015;36(5): 297-306.
18. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351(13):1296-305.
19. Wizemann V, Tong L, Satayathum S, et al. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. Kidney Int 2010;77(12):1098-106.
20. Reinecke H, Brand E, Mesters R, et al. Dilemmas in the management of atrial fibrillation in chronic kidney disease. Clin J Am Soc Nephrol 2009;20(4):705-11.
21. Jalal DI, Chonchol M, Targher G. Disorders of hemostasis associated with chronic kidney disease. Semin Thromb Hemost 2010;36(1): 34-40.
22. Limdi NA, Beasley TM, Baird MF, et al. Kidney function influences warfarin responsiveness and hemorrhagic complications. Clin J Am Soc Nephrol 2009;20(4):912-21.
23. Sjogren V, Grzymala-Lubanski B, Renlund H, et al. Safety and efficacy of well managed warfarin. A report from the Swedish quality register Auricula. Thromb Haemost 2015;113(6):1370-7.
24. Piccini JP, Stevens SR, Chang Y, et al. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. Circulation 2013;127(2):224-32.
25. Herzog CA, Ma JZ, Collins AJ. Long-term survival of dialysis patients in the United States with prosthetic heart valves: should ACC/AHA practice guidelines on valve selection be modified? Circulation 2002;105(11):1336-41.
26. Umezu K, Saito S, Yamazaki K, et al. Cardiac valvular surgery in dialysis patients: comparison of surgical outcome for mechanical versus bioprosthetic valves. Gen Thorac Cardiovasc Surg 2009;57(4):197-202.
27. Chan V, Jamieson WR, Fleisher AG, et al. Valve replacement surgery in end-stage renal failure: mechanical prostheses versus bioprostheses. Ann Thorac Surg 2006;81(3):857-62.
28. Misawa Y. Heart valve replacement for patients with end-stage renal disease in Japan. Ann Thorac Cardiovasc Surg 2010;16(1):4-8.

Paper III

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Full Length Article

INR variability and outcomes in patients with mechanical heart valve prosthesis

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ABSTRACT

Background: The quality of treatment with warfarin is mainly assessed by the time in therapeutic range (TTR) in patients with mechanical heart valve prosthesis (MHV). Our aim was to evaluate if International Normalized Ratio (INR) variability predicted a combined endpoint of thromboembolism, major bleeding and death better than TTR.

Methods and results: We included 394 patients at one center with MHV during 2008–2011 with adverse events and death followed prospectively. TTR 2.0–4.0 and log-transformed INR variability was calculated for all patients. In order to make comparisons between the measures, the gradient of the risk per one standard deviation (SD) was assessed. INR variability performed equal as TTR 2.0–4.0 per one SD unit adjusted for covariates, hazard ratio (HR) 1.30 (95% CI 1.1–1.5) and 0.71 (95% CI 0.6–0.8) respectively for the combined endpoint, and performed better for mortality HR 1.47 (95% CI 1.1–1.9) and 0.70 (95% CI 0.6–0.8). INR variability was categorized into high and low group and TTR into tertiles. High variability within the low and high TTR, had a HR 2.0 (95% CI 1.7–3.6) and 2.2 (95% CI 1.1–4.1) respectively, of the combined endpoint compared to the low variability/high TTR group. INR values <2.0 greatly increased the rate of thromboembolism whereas the rate of major bleeding increased moderately between INR 3.0 and 4.0 and increased substantially after INR >4.0.

Conclusion: The INR variability is an equal predictor as TTR of the combined endpoint of thromboembolism, major bleeding and death, and adds important information on top of TTR in patients with MHV.

1. Background

In order to choose the optimum INR target range for patients with mechanical heart valve prosthesis (MHV), the guidelines recommend that valve model and patient risk factors should be considered. Given the gravity of the adverse events, paramount importance must be given to identify patients that are at highest risk. The time in therapeutic range (TTR) has in many studies been accepted as a surrogate marker for the quality of anticoagulation treatment given. A tight control of the anticoagulation treatment in terms of a high TTR reduces the risk of all complications and major bleeding events in patients with MHV [1] and is an important tool at anticoagulation clinics to assess the quality of anticoagulation treatment given.

The TTR assesses the time spent within the INR target range according to Rosendaal's method [2], not considering the variations of the obtained INR values within the target range. The variance growth rate initially described by Fihn [3] considered the time weighted variance of the INR around the target INR and reflects the degree to which a patient's achieved INR deviates from his or her target INR over a prolonged interval. Subsequently, Cannegieter et al. [4] and Fihn et al. [5] modified the formula which considered the variance of the INR achieved and did not depend on the target INR. Whereas TTR measures intensity of anticoagulation, variability measures the stability and variance (fluctuation) of anticoagulation. INR variability have been shown to predict thrombotic and bleeding events in patients with atrial fibrillation [3,6,7] and one recent study even demonstrated that INR variability predicts adverse events independent of TTR in patients with atrial fibrillation [8].

There have been few studies addressing these two measures of anticoagulation control and only one study involving patients with MHV [9], which showed that the model involving both variability and target INR was most clearly associated with complications of anticoagulant therapy compared to models with pure variability.

The importance of the measure INR variability on top of high TTR which is the most accepted surrogate marker for anticoagulation

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Table 1
Baseline characteristics.

	(n = 394)
Age (years)	70.3 (±14)
Male	226 (57)
AVR	270 (69)
MVR	107 (27)
AVR/MVR	17 (4)
Hypertension	240 (61)
Diabetes	60 (15)
Prior ischemic stroke	50 (13)
Prior major bleeding	47 (12)
Vascular disease	17 (4)
Atrial fibrillation	157 (40)
Heart failure	126 (32)
LVEF 35–50%	107 (27)
LVEF < 35%	19 (5)
eGFR	61.4 (±20)
Alcohol overconsumption	10 (3)
Liver failure	2 (1)
Antiplatelet drugs	12 (3)
TTR 2.0-4.0	90.9

Values are n (%) or means ± SD. AVR, aortic valve replacement; MVR, mitral valve replacement; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate (Lund-Malmö revised formula); TTR, time in therapeutic range.

therapy, is uncertain in patients with MHV. The object of the study was to evaluate the predictive effect of INR variability and a combined endpoint consisting of thromboembolism (TE), major bleeding and death in patients with MHV, and to investigate if using both INR variability and TTR will more accurately distinguish patients with increased risk of the combined endpoint. Further, we also intended to determine the rates of TE and major bleeding according to the intensity of anticoagulation to evaluate the optimal INR values for patients with MHV.

2. Method

All patients with MHV on anticoagulation treatment in Malmö, Sweden was prospectively followed and monitored in the Swedish national quality register for atrial fibrillation and anticoagulation, AuriculA, during 01/01/2008–31/12/2011. All outpatients who are treated with warfarin at these centers are referred to regional anticoagulation clinics to have their treatment monitored regularly in AuriculA. The register includes a web-based dosing program and decision support that uses an algorithm to calculate warfarin dosage based on the last two or three INR results [10].

The primary endpoint was a combined endpoint which consisted of TE, major bleeding and death which were recorded prospectively. TE was defined according to the guidelines for reporting mortality and morbidity after cardiac valve intervention [11], i.e. stroke, transient ischemic attack (TIA) or an embolus documented operatively, at autopsy, or clinically that produces signs or symptoms attributable to complete or partial obstruction of a peripheral artery. Major bleeding events were defined according to ISTH definitions [12] which included falls in hemoglobin levels of greater than 20 g/L, transfusion of ≥2 units, symptomatic bleeding in a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, as well as intramuscular with compartment syndrome) or fatal bleeding. A review of events was performed by one of the authors to ensure that complications were correctly classified. During the study period, the target INR range was 2.0–4.0 for all patients with MHVs irrespective of patient-related risk factors. All mortality data was extracted from AuriculA or medical records and in a few cases from the Swedish Cause of Death Register. Patients contributed with time at risk as long as they were receiving warfarin.

The INR variability was estimated by Fihn's method, which reflects the degree to which a patient's INR deviates from the previous one. This method does not take into account the intensity of the achieved INR results. We excluded patients with fewer than 5 INR samples and patients with discontinuation of warfarin due to terminal end-stage diseases. We included all INR measurements until the day of one of the events and excluded all INR values measured following an event. The INR measurement of the time of the event is included in the analysis. The duration of treatment within designated TTR levels (1.5–2.0, 2.0–2.5 etc.) was estimated and the incidence rates of major bleeding and TE were calculated according to the INR at time of event. This means that each TTR level contributes with time for the analysis of the incidence rates. There were some events where an INR measurement could not be estimated for these analyses.

In order to choose a cutoff point for high vs low variability we examined the Log INR variability by quintiles and investigated the primary endpoints in a Cox regression analysis. A clinical relevant cutoff point was determined (fourth quintile; >− 0.43) in order to dichotomize high vs low INR variability for further analyses in the cohort. The TTR 2.0–4.0 was divided into tertiles based on the distribution of the cohort which consisted of a high TTR. Under these circumstances, the tertiles were TTR (<89.1%, 89.1–96.0%, >96.0%). This approach which reflects the distribution ensures that a sufficient number of patients and events are included in the groups and facilitates the analyses.

The study was approved by the Regional Ethical Review Board at Lund University.

3. Statistics

TTR was calculated according to Rosendaal's method which uses linear interpolation to assign an INR value to each day between successive observed INR values [2]. INR variability was calculated using Fihn's method which only considers the achieved INR value deviation from the previous one and accordingly considers pure INR variability [5]. The INR variability was logarithmically transformed due to skewed distributions and to minimize influence of extreme observations. The linear association between TTR and log INR variability was estimated by calculation of the Pearson correlation coefficient value. The INR variability and TTR was separately analyzed in a Cox proportional-hazards regression analysis with the beta coefficient expressed per one standard deviation (SD) increase of each factor in order to allow comparison between the predicting variables. Univariate analysis was performed and statistically significant covariates were included in the multivariate analysis. We chose a cutoff point for log INR variability (>− 0.43) based on the cox regression analysis where the combined endpoint was significantly increased compared to the lowest log INR variability quintile. In the last cox regression analysis, we included both measures of log INR variability and TTR to assess age-adjusted hazard of log INR

Table 2
Log INR variability quintiles with crude hazards for outcome events, compared with the lowest variability quintile as reference.

Log INR variability quintiles	n	Age	TTR 2.0–4.0	Log INR variability	Combined endpoint	Thromboembolism	Major bleeding	Death
1	74	70.8 (±14)	97.9	−2.56	Ref	Ref	Ref	Ref
2	85	68.0 (±14)	94.4	−1.41	0.8 (0.4–1.6)	0.6 (0.1–3.6)	1.4 (0.9–3.7)	0.7 (0.3–1.6)
3	77	68.8 (±15)	91.9	−0.77	1.3 (0.7–2.4)	2.6 (0.7–9.8)	2.1 (0.9–5.1)	0.6 (0.2–1.5)
4	79	71.8 (±14)	87.4	0.02	1.6 (0.9–2.9)	1.8 (0.4–7.5)	2.2 (0.9–5.4)	1.5 (0.7–3.3)
5	79	73.0 (±14)	82.9	1.04	2.6 (1.5–4.6)	3.0 (0.8–11.4)	2.5 (1.01–6.1)	2.7 (1.3–5.4)

Values are means (±SD) or hazard ratio (95% CI).

Table 3
The predictive ability of the Log INR variability and TTR (2.0–4.0) expressed per one standard deviation (SD) change of each variable.

	Hazard ratio (95% CI) per a change of 1 SD of the predicting variable			
	Combined endpoint	Thromboembolism	Major bleeding	Death
Log INR Variability	1.30 (1.11–1.52)	1.55 (1.03–2.34)	1.20 (0.93–1.57)	1.47 (1.11–1.93)
TTR 2.0–4.0	0.71 (0.61–0.83)	0.86 (0.62–1.20)	0.61 (0.49–0.77)	0.70 (0.58–0.83)

Major bleeding was adjusted for age, hypertension and eGFR. Death was adjusted for age, hypertension, diabetes, eGFR and time since valve replacement. The combined endpoint was adjusted for age, hypertension, diabetes, eGFR, heart failure and time since valve replacement.

variability within different levels of TTR, compared to the theoretical best group (low INR variability/high TTR). All tests were performed two-tailed, and a p-value of <0.05 was considered significant. Incidence rates per 100 patient-years were calculated using the Person Time module in OpenEpi, version 3.03 (www.openepi.com). All other analyses were performed using SPSS Statistics (Version 22.0; SPSS Inc., IBM corporation, Armonk, NY).

4. Results

4.1. Baseline characteristics

The primary cohort consisted of 407 patients, with 13 patients excluded from baseline which yielded 394 patients. The 13 patients were excluded because of few INR measurements to estimate INR variability and TTR. Our cohort was predominantly patients with aortic valve replacement (AVR) (69%) with a mean age of 70 years and a TTR 2.0–4.0 of 91% (Table 1). The achieved mean INR ($\pm$SD) was 2.85 ($\pm$0.25) for AVR and 2.89 ($\pm$0.22) for mitral valve replacement (MVR). During the study period, a total of 18.852 INR values were obtained from AuriculA for the analyses of TTR and variability, and an accrued total of 1348 patient-years of monitoring. There were a total of 122 cases of the combined endpoint, with 62 major bleeding events, 26 TE events and 68 deaths. Of the major bleeding events, five patients were under bridging therapy with low-molecular weight heparin (LMWH), two patients which suffered from an event abroad where an INR measurement at the time of the event could not be found after transferring to the belonging hospital and one patent where no INR measurement was taken during the first day. Of the TE-events, four patients were under treatment with LMWH when the event occurred. These cases were excluded in this specific analysis.

4.2. Characteristics of INR variability and TTR

By separating the Log INR variability by quintiles, hazard ratios (HR) for our primary endpoints were calculated (Table 2). As the quintiles increased in variability, the TTR tended to decrease with increasing age except for in the first quintile ($p < 0.001$ for trend). For each increase in the variability quintile, the incidence rate of the combined endpoint tended to increase and was 6.8, 5.4, 8.8, 10.1 and 15.2 per 100 patient-years respectively. The combined endpoint, major bleeding and death had a significantly increased hazard in the last quintile with a borderline significant trend in the fourth quintile for the combined endpoint. Based on this table, the Log INR variability of >-0.43 was chosen to differentiate the high vs low variability in our cohort. With this cutoff point, 40% of the cohort had high variability (unstable anticoagulation). The TTR 2.0–4.0 was divided into three equal groups for further analysis, which yielded tertiles of $<89.1\%$, 89.1%–96.0% and $>96.0\%$. The Pearson correlation between TTR and Log INR variability was -0.57 ($p < 0.001$) indicating a moderate correlation.

4.3. Independent predictive ability of INR variability and TTR 2.0–4.0

The predictive ability of Log INR variability and TTR 2.0–4.0 for the combined endpoint, major bleeding, TE and death were examined by expressing the variables as the gradient of risk per one SD of the respective variable adjusted for the appropriate covariates (Table 3). For every one SD increase in the Log variability, the combined endpoint, TE and mortality increased by 30%, 55% and 47% respectively. Simultaneously, per one SD increase of TTR 2.0–4.0 the combined endpoint, major bleeding and mortality by decreased by 29%, 39% and 30% respectively. There was an evident trend between Log INR variability and major bleeding, whereas no association was found between TTR 2.0–4.0 and TE.

4.4. High vs low INR variability within different TTR levels

In order to investigate both anticoagulation measures in the same model we performed an analysis where high and low variability were examined in all three TTR levels compared to the hypothetical best group (high TTR-low variability) in an age-adjusted model (Table 4). The high variability within the low and high TTR were significantly associated with increased risk of the combined endpoint compared to the low variability/high TTR group, whereas the high variability within the moderate TTR was not significant. As for mortality, high variability in the low TTR group was significant while there was a trend for higher hazard in the high variability groups within the remaining TTR levels. For major bleeding and TE, no obvious trend towards higher hazard in the high variability groups could be found.

4.5. Intensity of anticoagulation and rates of major bleeding and TE

In order to illustrate the distribution of time spent within the various INR ranges and the clinical sequelae of the INR measurements, we calculated the incidence rates of major bleeding and TE were calculated according to the INR at time of event (Fig. 1). The incidence rates for each designated INR interval, and for AVR and MVR are presented in Table 5. The rate of TE was highest at the lowest INR values and was evened at INR values >2.5. The rate of major bleeding increased slightly between the ranges 3.0–4.0 which further increased substantially after INR >4.0. The INR on admission for major bleeding was <4.0 for 59%

Table 4
Age-adjusted hazard ratios for different levels of TTR (high–moderate–low) and Log INR variability (high and low) compared to high TTR–low variability group.

	Combined endpoint	TE	Major bleeding	Death
Low TTR–high variability	2.0 (1.7–3.6)	1.9 (0.6–6.2)	2.2 (0.9–5.0)	2.2 (1.1–4.4)
Low TTR–low variability	1.4 (0.8–2.7)	1.6 (0.5–5.6)	2.2 (0.9–5.3)	0.9 (0.4–2.3)
Moderate TTR–high variability	1.5 (0.8–2.7)	1.7 (0.4–6.2)	1.9 (0.7–4.8)	1.1 (0.5–2.5)
Moderate TTR–low variability	0.9 (0.5–1.6)	0.7 (0.2–2.8)	1.7 (0.7–3.9)	0.4 (0.2–1.2)
High TTR–high variability	2.2 (1.1–4.1)	1.8 (0.4–7.6)	2.2 (0.8–5.8)	1.6 (0.7–3.7)
High TTR–low variability	Ref	Ref	Ref	Ref

Age-adjusted HR (95% CI); TE, thromboembolism.

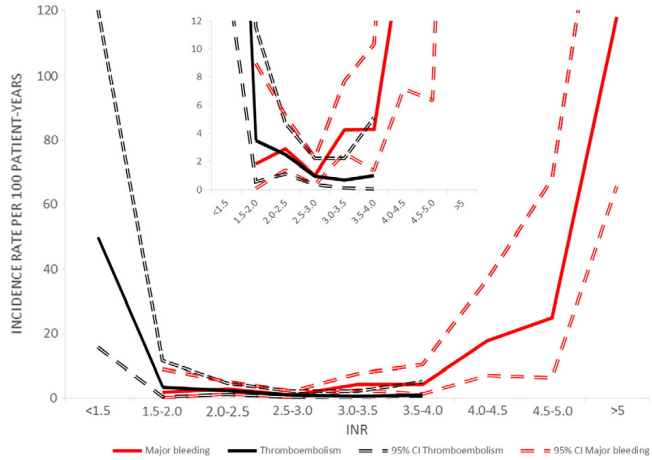

Fig. 1. Rate of major bleeding and thromboembolism according to the INR at the time of event in relation to duration of treatment within designated INR ranges. Incidence rates taken from Table 5. Upper image, an enlargement with scaled incidence rate. Major bleeding defined according to ISTH and thromboembolism according to the guidelines for reporting mortality and morbidity after cardiac valve intervention.

of the cases, and >5.0 for 24%. The INR on admission for TE was <2.0 for 27% of the cases, and 2.0–4.0 for the remaining cases (73%). The incidence of TE was 1.5 higher for MVR than AVR, although without statistical significance.

5. Discussion

The result of this study shows that the variability of INR, which measures another aspect of anticoagulation control, namely the stability and not the intensity of INR, is a significant predictor of a combined endpoint in patients with MHV. We demonstrate that the Log INR variability expressed per one SD has an equal predictive ability as TTR 2.0–4.0 for the combined endpoint and performs even better for mortality. Secondly, our results indicate that the risk of suffering from the combined endpoint within different levels of TTR is influenced significantly by high INR variability.

In order to make relevant comparisons between the anticoagulation measures INR variability and TTR, we used the gradient of risk per SD in the predictive analysis. The Log INR variability performed equally as TTR 2.0–4.0 (HR: 1.30 and 0.71 respectively) for the combined endpoint, while there were some differences for the remaining endpoints. The significant association between TE and Log INR variability may reflect the fact that the majority of the TE event (73%) occurred during INR 2.0–4.0 which implies that few subtherapeutic measurements are liable for the TE events, and that the Log INR variability is a more sensitive predictor of TE in patients with MHV. The Log INR variability even performed better than TTR 2.0–4.0 for mortality which usually is considered as the most important single endpoint compared to nonfatal endpoints. Similarly, 40% of the INR on admission was supratherapeutic (>4.0) which supports the significant predictive ability of TTR 2.0–4.0 for major bleeding. It seems that higher variability within therapeutic ranges in our cohort does not influence the risk of major bleeding events.

Table 5
Incidence rates of major bleeding and thromboembolism according to the INR at the time of event reflecting Fig. 1.

INR	Rate major bleeding	Rate thromboembolism
<1.5		50 (15.9–121)
1.5–2.0	1.8 (0.1–9.0)	3.5 (0.6–11.6)
2.0–2.5	2.9 (1.4–5.3)	2.5 (1.2–4.7)
2.5–3.0	1.0 (0.4–2.3)	1.0 (0.4–2.2)
3.0–3.5	4.3 (2.6–7.7)	0.7 (0.1–2.2)
3.5–4.0	4.3 (1.4–10.4)	1.0 (0.1–5.1)
4.0–4.5	17.7 (7.2–36.7)	
4.5–5.0	25.0 (6.4–68.0)	
>5	118 (66–197)	
AVR	5.2 (3.9–6.9)[a]	1.8 (1.0–2.8)[a]
MVR	4.8 (2.8–7.6)	2.6 (1.3–4.8)

Incidence rate (95% CI); per 100 patient-years; AVR, aortic valve replacement; MVR, mitral valve replacement.
[a] Not significant compared to MVR.

High INR variability had at all TTR levels an obvious trend towards higher rates of the combined endpoint, and was significant in the low and high TTR level. An obvious trend for death was found in the same manners. This suggests that variability beyond the predictive ability of TTR can provide additional prediction of adverse events, and that aiming for higher levels of TTR in order to reduce adverse events and death may be insufficient if INR variability is high. The variability should be evaluated in the context of a tight anticoagulation control, given that the lowest tertile had a mean TTR of 81%, which indicates that the effect of INR variability is substantial at all TTR levels. The hazards of high INR variability within the various TTR levels were not significant for major bleeding and TE in our cohort and could be attributable to the sample size and statistical power.

Razouki et al. [8] showed that the Log INR variability and TTR independently predicted adverse events and that high INR variability within fixed levels of TTR was associated with higher risk of adverse events in a retrospective cohort of patients with atrial fibrillation. However, this study used registers and automated data to extract patient-related risk factors and outcomes, and were not validated nor prospectively registered as in our study, and estimated TTR of 2.0–3.0. Our results which constitutes of patients with MHV concur with this study that INR variability is a risk factor per se, added to the risk that TTR is carried with. Although the target range of 2.0–4.0 was used in our cohort, calculation with TTR 2.0–3.0 was made for all endpoints which did not result in any significant association to neither endpoint. This is probably due to the fact that another INR interval was used and that a sufficient number of

the obtained INR values were outside this interval which may have diluted any correlation to the different endpoints.

van Leeuween et al. [9] showed in a case–control study in patients with MHV, that INR variability and TTR 2.5-4.0, primarily 3 months prior to an event could be associated with an increased risk of hemorrhagic and thrombotic complications. However, these results were not adjusted for other significant variables which could affect outcomes and did not investigate the effect of INR variability in different levels of TTR. Further, the INR variability was dichotomized for all analyses which causes considerable loss of power and residual confounding.

At the moment, no validated cut-off value for INR variability exists to distinguish between high vs low values. We chose our cut-off value based on the combined endpoint that increased beyond this threshold while Razouki et al. [8] selected a different cut-off value based on their datasets in patients with atrial fibrillation. Clearly, more data and studies are required in different data sets in patients with MHV to determine a threshold in INR variability to be adopted in the clinic.

Previous studies have demonstrated that the incidence of stroke and intracranial bleeding in patients with atrial fibrillation is greatly increased when INR decline below 2.0 and when INR exceeds 4.0 respectively [13–16]. We demonstrate a similar pattern in patients with MHV, with an increasing incidence rate of major bleeding, in particular when INR exceeds 4.0. As for the TE events, an inversely decreasing incidence is demonstrated with high incidence rates for INR < 1.5, whilst the rate was balanced out for INR > 2.5. This could imply that revising target INR upwards considering patient risk factors (previous TE, atrial fibrillation, MVR or tricuspid valve replacement, heart failure, mitral stenosis) according to the European guidelines, is performed at the expense of higher rates of bleeding without reducing the risk of TE. In addition, four patients which constituted a substantial amount of the TEs, had undergoing bridging therapy with LMWH, suffered from a TE event (not included in the analysis) which is remarkable. The European guidelines recommend interruption of anticoagulant therapy for major surgical procedures and an INR < 1.5 and bridging with heparin, with only a level of evidence C [17].

Our results suggest that in order to evaluate the quality of anticoagulation therapy further, INR variability should be monitored along with TTR, and increasing the frequency of INR monitoring in patients with high INR variability might reduce the risk of adverse events in patients with MHV. There is support that increasing INR measurements in patients with MHV reduce the INR variability, which is shown for patients on self-monitoring [18]. This particularly concerns patients with chronic kidney disease due to the poorer anticoagulation control and increased adverse events and death in this group [19]. Obviously, future studies are required to evaluate if reducing INR variability will decrease the risk of clinical adverse events.

There were some limitations in the study that needs to be acknowledged. The target INR range of 2.0–4.0 was used for all types of MHVs during the study period which is not recommended in the guidelines anymore. However, the widened target range facilitates the estimation of the INR variability to obtain statistical power for the primary endpoints and further, the achieved mean INR was 2.86. The Log INR variability would have been more robust with a larger cohort which would have yielded a more accurate threshold for distinguishing the adverse events. However, our study was strengthened by the prospective registration of the adverse events, known baseline risk factors which can be adjusted for in the analysis, the ability to characterize periods with bridging therapy in time of event which affect results for INR variability and INR-dependent incidence rates and the fact that all patients with MHV from one center was included without exclusion criteria's which is clinically relevant.

In conclusion, the INR variability which measures the anticoagulation stability rather than intensity (TTR), is an equal predictor as TTR 2.0–4.0 of a combined endpoint, and adds important information on top of TTR in patients with MHV. Addressing high TTR may not be sufficient in reducing adverse events if INR variability is high which may suggest that monitoring INR variability in addition to TTR in these patients can be recommended.

Conflict of interest

None declared.

Acknowledgments

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References

[1] B. Grzymala-Lubanski, A. Labaf, E. Englund, P.J. Svensson, A. Sjalander, Mechanical heart valve prosthesis and warfarin — treatment quality and prognosis, Thromb. Res. 133 (2014) 795–798.
[2] F.R. Rosendaal, S.C. Cannegieter, F.J. van der Meer, E. Briet, A method to determine the optimal intensity of oral anticoagulant therapy, Thromb. Haemost. 69 (1993) 236–239.
[3] S.D. Fihn, M. McDonell, D. Martin, J. Henikoff, D. Vermes, D. Kent, et al., Risk factors for complications of chronic anticoagulation: a multicenter study, Ann. Intern. Med. 118 (1993) 511–520.
[4] S.C. Cannegieter, F.R. Rosendaal, A.R. Wintzen, F.J. van der Meer, J.P. Vandenbroucke, E. Briet, Optimal oral anticoagulant therapy in patients with mechanical heart valves, N. Engl. J. Med. 333 (1995) 11–17.
[5] S.D. Fihn, C.M. Callahan, D.C. Martin, M.B. McDonell, J.G. Henikoff, R.H. White, The risk for and severity of bleeding complications in elderly patients treated with warfarin. The National Consortium of Anticoagulation Clinics, Ann. Intern. Med. 124 (1996) 970–979.
[6] M. Lind, M. Fahlen, M. Kosiborod, B. Eliasson, A. Oden, Variability of INR and its relationship with mortality, stroke, bleeding and hospitalisations in patients with atrial fibrillation, Thromb. Res. 129 (2012) 32–35.
[7] S. Ibrahim, J. Jespersen, L. Poller, European Action on A, The clinical evaluation of International Normalized Ratio variability and control in conventional oral anticoagulant administration by use of the variance growth rate, Journal of Thrombosis and Haemostasis: JTH 11 (2013) 1540–1546.
[8] Z. Razouki, A. Ozonoff, S. Zhao, G.K. Jasuja, A.J. Rose, Improving quality measurement for anticoagulation: adding international normalized ratio variability to percent time in therapeutic range, Circulation Cardiovascular Quality and Outcomes 7 (2014) 664–669.
[9] Y. van Leeuwen, F.R. Rosendaal, S.C. Cannegieter, Prediction of hemorrhagic and thrombotic events in patients with mechanical heart valve prostheses treated with oral anticoagulants, Journal of Thrombosis and Haemostasis: JTH 6 (2008) 451–456.
[10] B. Grzymala-Lubanski, S. Själander, H. Renlund, P.J. Svensson, A. Själander, Computer aided warfarin dosing in the Swedish national quality registry AuriculA — algorithmic suggestions are performing better than manually changed doses, Thromb. Res. 131 (2013) 130–134.
[11] C.W. Akins, D.C. Miller, M.I. Turina, N.T. Kouchoukos, E.H. Blackstone, G.L. Grunkemeier, et al., Guidelines for reporting mortality and morbidity after cardiac valve interventions, J. Thorac. Cardiovasc. Surg. 135 (2008) 732–738.
[12] S. Schulman, C. Kearon, the SOCOAOTS, Standardization Committee Of The International Society On T, Haemostasis, Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients, J. Thromb. Haemost. 3 (2005) 692–694.
[13] E.M. Hylek, D.E. Singer, Risk factors for intracranial hemorrhage in outpatients taking warfarin, Ann. Intern. Med. 120 (1994) 897–902.
[14] E.M. Hylek, A.S. Go, Y. Chang, N.G. Jensvold, L.E. Henault, J.V. Selby, et al., Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation, N. Engl. J. Med. 349 (2003) 1019–1026.
[15] A. Oden, M. Fahlen, R.G. Hart, Optimal INR for prevention of stroke and death in atrial fibrillation: a critical appraisal, Thromb. Res. 117 (2006) 493–499.
[16] S.C. Cannegieter, M. Torn, F.R. Rosendaal, Oral anticoagulant treatment in patients with mechanical heart valves: how to reduce the risk of thromboembolic and bleeding complications, J. Intern. Med. 245 (1999) 369–374.
[17] J. Taylor, ESC/EACTS guidelines on the management of valvular heart disease, Eur. Heart J. 33 (2012) 2371–2372.
[18] C. Dauphin, B. Legault, P. Jaffeux, P. Motreff, K. Azarnoush, H. Joly, et al., Comparison of INR stability between self-monitoring and standard laboratory method: preliminary results of a prospective study in 67 mechanical heart valve patients, Archives of Cardiovascular Diseases 101 (2008) 753–761.
[19] A. Labaf, B. Grzymala-Lubanski, A. Sjalander, P.J. Svensson, M. Stagmo, Glomerular filtration rate and association to stroke, major bleeding, and death in patients with mechanical heart valve prosthesis, Am. Heart J. 170 (2015) 559–565.

Paper IV

Incidence and risk factors for thromboembolism and major bleeding in patients with mechanical valve prosthesis; a nationwide population-based study

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Background:

Risk factors of stroke/thromboembolism (TE) and major bleeding, and incidence of these events in specific age categories in warfarin-treated patients with mechanical heart valves (MHV) are uncertain. Our objective was to calculate event rates in specific age categories and identify risk factors for adverse events.

Methods and results:

We identified 4,810 treatment periods with MHV between January 2006 and December 2011 in the Auricula and SWEDEHEART registries. There were 3,751 treatment periods with aortic valve replacements (AVR) and 866 with mitral valve replacements (MVR). Median follow-up time was 4.5 years (IQR: 1.5-6.0). Time in therapeutic range (TTR) with warfarin for patients with AVR was 74.2% for INR 2.0-3.0, with 72% of the patients having this target range. Rate of stroke/TE for AVR and MVR was 1.3 and 1.6 per 100 patient-years respectively (p=0.20). The rate of first major bleeding was 2.6 and 3.9 per 100 patient-years with AVR and MVR respectively (p <0.001). By multivariate analysis for AVR, age (HR: 1.02; CI 1.01-1.03 per year) and previous stroke (HR: 2.4;CI 1.7-3.5) emerged as independent risk factors for stroke/TE. Heart failure (HR: 0.9;CI 0.6-1.4) and atrial fibrillation (HR: 1.0;CI 0.7-1.4) were not associated to stroke/TE. For major bleeding events, age (HR: 1.02;CI 1.01-1.03 per year) and previous major bleeding (HR: 2.5;CI 1.9-3.3) emerged as independent risk factors for AVR.

Conclusions:

In a nationwide cohort study with MHV and high TTR, heart failure and atrial fibrillation did not appear as risk factors of stroke/TE.

Introduction

Studies with newer generation mechanical heart valves (MHV) reports low incidences of thromboembolic (TE) episodes and bleeding events in patients with low target INR ranges (1, 2). However, the studies were underpowered to demonstrate superiority over higher INR target ranges, possibly due to the low burden of comorbidity and young age of the patients enrolled. Thus, guideline recommendations regarding target ranges have not been revised compared to previous versions.

There is still controversy over patient-related risk factors and the extent of impact they should have on target INR. Many studies addressing this issue have various target ranges and quality of anticoagulation treatment that could influence the results. In light of these conditions, European and American guidelines recommend an INR target of 3.0 in patients with aortic valve replacement (AVR) and additional risk factors for TE (3-5). The risk factors included in the guidelines are atrial fibrillation, previous TE, left ventricular dysfunction and hypercoagulable condition. There is however, no evidence that revising INR upwards in patients with these additional risk factors will decrease the risk of TE. These recommendations are solely based on a review article (6), which further is based on the authors' own experience on TE-events and a few studies from the 70-90s. It is important to emphasize that newer generation valves are much less prone to thrombus formation, and clearly not all TE-events in patients with MHV are related to the prosthetic valve inserted, hence to a varying degree associated with other patient-related risk factors.

Several randomized trials have demonstrated that lower target INR, compared to standard target INR, is associated to lower bleeding rates with similar risk of TE, at least in low-risk aortic MHV patients (2, 7, 8). In Sweden, INR target is generally not revised upwards in presence of risk factors included in the guidelines.

In the present study, we aimed to identify risk factors associated with TE and major bleeding and the rate of these adverse events within different age categories in patients with MHV, in a large contemporary unselected cohort with a high quality of the warfarin-treatment.

Methods

Data sources

Approximately half of the Swedish anticoagulation centers are included in Auricula, the Swedish national quality registry for atrial fibrillation and patients treated with oral anticoagulants. Over 120,000 patients are currently (2015) followed in Auricula (9). The register includes key patient characteristics, risk factors for TE, current treatment and previous treatments of oral anticoagulation. Key outcome measures are TE and major bleeding events that are requested annually, as well as at the end of each treatment period. Auricula includes a web-based dosing program and decision support that uses an algorithm to calculate warfarin dosage based on the last two INR results. Since all patients requiring warfarin treatment in these centers are included in Auricula, no patient escapes registration in the study.

Information about baseline patient characteristics and outcomes were extracted from the National Patient Registry covering all diagnoses recorded in the patient's medical records within hospitals throughout Sweden, for outpatient as well as inpatient care. It does not cover primary care. Further, information regarding prosthesis choice, size, diagnose code for surgery and date of surgery was extracted from the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry. This register covers all patients undergoing coronary angiography, angioplasty, or cardiac surgery in Sweden. The details of the register have been previously published (10). The present study cohort was created by merging data in Auricula with the National Patient Register and SWEDEHEART, creating a cohort of 4,810 treatment periods consisting of 3,916 patients.

Study definitions

The study period ranged from January 1, 2006 until December 31, 2011. Every treatment period registered in Auricula was given an individual identification number. Within the study period, patients could have any number of treatment periods. For instance, a valve replacement in a patient with treatment of warfarin from a different indication will count as a new treatment period. Also a change of target INR will count as a new period. For treatment that started before or continued after the study

period, start and end dates were set to the study's start and end dates. We defined ICD-10 codes that constituted a complication (see appendix). Drugs prescribed six months before the start of the study were registered for each patient but not included in the multivariate analysis. Major bleeding was defined as an event requiring hospital admission due to bleeding, with an ICD-10 code as listed in the appendix. The bleedings were divided into intracranial, gastrointestinal and other bleeds. TE-events were defined as clinically verified arterial thrombosis and included stroke, transient ischemic attack (TIA) and systemic embolism. The reported mortality excludes mortality during the index hospitalization, i.e at the time of the heart surgery, since patients who died in hospital never reached an anticoagulation clinic for inclusion in Auricula.

Time was calculated during the study period until a first complication of every specified type occurred. For every treatment period and patient, time until complication was calculated for every defined type of complication.
Contribution of any and all types of complications was permitted during the study period. However, in order to reduce the risk of overrating we allowed only one complication of every subtype per treatment period. Hence the rate was defined as the first major bleeding or stroke/TE, or the total of every specified type of that endpoint. For instance, if a patient suffered from a gastrointestinal bleeding and an intracranial bleeding further on, the rate of first major bleeding includes the gastrointestinal bleeding whereas the total rate accounts for both endpoints.

We used only primary diagnoses of cerebral hemorrhage or infarction, due to the risk of over-registering the repeated use of an ICD-10 code at subsequent contacts.
The translation of ICD-10 was completed and started in 1998 in Sweden.
Some patients (n=358) underwent the valve replacement between 1992-1997, hence using ICD-9 codes for the preoperative risk factors, which we did not have access to. Furthermore, there were 37 patients that had no preoperative diagnose codes. These patients can underestimate the occurrence of patient risk factors and can dilute results and patient characteristics. Consequently, these patients (n=395) that did not have any registered ICD-10 codes preoperatively were excluded from the multivariate analyses, but not in the event rates. The study was approved by the regional ethical review board in Umeå (EPN nr 2011-349-31 M).

Statistics

Continuous variables are presented as mean ± SD or median and interquartile range (IQR). Categorical variables are presented as percentage of the sample. Incidence rates are reported per treatment year with confidence intervals of 95%, and time contributed within each age span of 10 years was calculated with the patient's age at the time of event in the analysis. Univariate analysis of preoperative patient characteristics for the entire cohort of AVR was performed, and statistically significant covariates and risk factors with known association to the outcomes were included in the multivariate Cox regression model. Besides age and sex, diabetes, hypertension, atrial fibrillation, heart failure, kidney failure, vascular disease and previous stroke were included as covariates for stroke/TE. For major bleeding, risk factors in the bleeding risk score HAS-BLED was used, namely age, hypertension, kidney failure, alcohol overconsumption, liver failure, previous stroke and previous major bleeding. Time since valve replacement until the start of the study period was also included in the multivariate analysis since patients had different dates for surgery. P-values < 0.05 were considered as significant. All statistical analyses were calculated with SPSS Statistics (version 22.0; SPSS, Inc, IBM Corporation, Armonk, NY) and R version 3.1.14, R Foundation for statistical Computing, Vienna, Austria. URL http://www.R-project.org/.

Results

General

Our study included 4,810 treatment periods (mean age 63.3 years, 31% female) that constituted of 3,751 AVR, 866 mitral valve replacements (MVR) and 193 with combined AVR/MVR, with 18,362 patient-years of data. Median follow-up time was 4.5 years (IQR 1.5-6 years). The distribution of preoperative baseline characteristics is shown in Table 1. Patients with AVR had significantly higher proportion of $P2Y_{12}$ inhibitors, aspirin, previous stroke and hypertension than patients with MVR. Conversely, patients with MVR had higher proportion of atrial fibrillation, heart failure, vascular disease and females. A total of 1,460 (30%) treatment periods were started (received a MHV) during the study period. There were 987 patients that received an isolated AVR during the study period, 145 patients received a MVR and 43 a combined AVR/MVR. A total of 244 strokes/TE, 587 major bleeding events and 371 deaths occurred in the entire cohort.

Stroke/TE

The rate of stroke/TE for patients with AVR and MVR are presented in table 2. The rate of stroke/TE in relation to different age categories in patients with AVR showed a linear trend towards increasing rates with increasing age (figure 1a). The event rate increased slightly until 70 years of age, and then increased substantially. The rate for patients with AVR between 60-70 years and 70-80 years was 1.0 and 1.7 per 100 patient-years, respectively (p =0.004). Similarly, the rate of stroke/TE in patients with MVR indicates a rise after 70 years of age and subsequently increased considerably (figure 2a). The event rate for 60-70 and 70-80 years was 1.5 per 100 patient-years for both groups. Patients with isolated AVR had a stroke/TE risk of 1.2 per 100 patient-years (CI 1.0-1.5) versus patients with AVR and concomitant coronary by-pass surgery (CABG) 1.6 per 100 patient-years (CI 1.2-2.2), p =0.08.

Major bleeding

A total of 587 major bleeding events occurred; 196 gastrointestinal, 92 intracranial and 299 other bleeding events. The rates of first and total major bleeding with AVR, and MVR are presented in table 2. The rate of first major bleeding events for AVR and MVR are plotted against age categories in figure 1b and 2b, where the rate is

comparable between 40-70 years of age and subsequently rises considerably. The rate for patients with AVR between 60-70 and 70-80 years was 2.2 and 2.9 per 100 patient-years (p=0.05) respectively. The rate for patients with MVR between 60-70 and 70-80 years was 2.6 and 4.1 per 100 patient-years (p=0.10) respectively.

Survival

Overall mortality during follow-up was 8.9% (281/3170) for AVR, 11.9% (71/598) for MVR and 12.8% (19/148) for combined AVR/MVR. For patients with MVR, unadjusted hazard ratio for mortality was 1.68 (CI 1.35-2.09), p <0.001 compared to AVR patients. Actuarial survival with AVR at 1, 3 and 5 years were 98.0%, 96.2% and 91.9%, for 987 patients that received an isolated AVR during the study period, and for MVR 93.3%, 91.5% and 85.8%, respectively for 145 patients that received a MVR during the study period.

Target INR and TTR

There was a wide variation of target ranges throughout the cohort, mostly due to local traditions and individual assessments. For 3,656 treatment periods with AVR (95 patients with insufficient INR data), time in therapeutic range (TTR) for INR 2.0-3.0 irrespective of their actual target range was 74.2%, with 74% of the patients having this INR target range. The target range of 2.5-3.5 and 2.0-4.0 was prescribed for 4.3% and 11.3% respectively of the patients with AVR. The proportion of atrial fibrillation was 26.0% and 22.4% (p=0.35) for the INR target ranges of 2.0-3.0 and 2.5-3.5 respectively, for heart failure 20.1% and 20.5% (p=0.92), and for previous stroke 10.0% and 14.3% (p=0.11) respectively.

For 866 treatment periods with MVR, TTR for INR target range 2.0-3.0 was 67.2%, in which 52% of the patients had this INR target. The target range of 2.5-3.5 and 2.0-4.0 was prescribed for 21.5% and 15.2% respectively.

The incidence of stroke/TE and major bleeding events within the target range 2.0-3.0 vs. 2.5-3.5 and 2.0-4.0 are presented in table 3. There were no significant difference in stroke/TE and major bleeding between the target ranges in AVR and MVR.

Risk factors for adverse events and mortality

On univariate analysis for patients with AVR, only age and previous stroke/TIA emerged as risk factors for stroke/TE, Table 3. Variables deemed to be clinically

important risk factors for stroke/TE or bleeding were included in the corresponding multivariate analysis. Regarding mortality, the variables used for stroke/TE and major bleeding were all significant on the univariate analysis and were therefore included in the multivariate analysis. Independent risk factors for mortality were age, hazard ratio (HR): 1.08; (95% confidence interval (CI): 1.07-1.10) per year, $p<0.001$, diabetes, HR: 1.76; (1.3-2.4), $p<0.001$, hypertension, HR: 1.32; (1.03-1.7), $p=0.03$, atrial fibrillation, HR: 1.42, (1.1-1.9), $p=0.008$, heart failure, HR: 1.55, (1.2-2.0), $p=0.001$, vascular disease, HR: 1.52, (1.05-2.2), $p=0.03$, kidney failure, HR: 3.24, (2.0-5.2), $p<0.001$.

Discussion

Current anticoagulation guidelines for patients with MHVs include both target levels and suggestions to adjust the levels upwards in the presence of other risk factors for thromboembolic disease. However, the guidelines have low level of evidence and are based on studies performed over 20 years ago and it is not clear if these recommendations still are valid. There is thus a need for contemporary studies to identify usable risk factors in large patient cohorts, with sufficient statistical power and acceptable anticoagulation quality.

One of the major findings of the study was that only previous stroke/TIA and age emerged as independent risk factors for stroke/TE. Previously identified risk factors, as atrial fibrillation and heart failure that are considered to increase the risk of thrombosis did not even show a trend toward association with stroke/TE. Similar results have also been reported from a small prospective cohort study in a setting with high TTR (11). Clinicians and anticoagulation clinics in Sweden appears to be reluctant to revise INR target upwards in presence of these risk factors, which was reflected in the present study in the similar proportions of risk factors between the different target ranges. Guidelines recommendations are based on limited data and should be interpreted in the context of the few and outdated studies that demonstrated increased risk of TE in presence of these risk factors (6). Inferior anticoagulation quality with wide-ranged target INR-levels with older generation MHV could have contributed to these findings. Furthermore, our present findings are important since the more recent studies on the subject (2,7,8) have been underpowered to establish a correlation with any patient-related risk factor.

The intensity of anticoagulation should be optimized so that protection from TE is achieved without excess risk of bleeding. Several studies have demonstrated that the risk of bleeding outweighs the risk of TE within standard target INR (1, 2, 7, 8), while it is more balanced in the lower target values. The incidences of stroke/TE were very similar in both valve positions between the different target ranges in our study, which also oppose recommendations of generally revising INR upwards. The doubled risk of bleeding compared to stroke/TE in all type of valves in our cohort suggests that aiming towards higher target INR values will most likely increase the bleeding risk further, without certainly decreasing the risk of thrombosis. It must be emphasized

that the quality of anticoagulation control determines the risk of anticoagulation-related complications and death in MHV patients (12, 13). Consequently, strict anticoagulation control in terms of high TTR, may explain that certain proposed risk factors were not associated to stroke/TE in our cohort.

Kidney failure is a strong predictor of major bleeding in patients with MHV and is associated with inferior anticoagulation control (14), whereas previous bleeding and age are well-known predictors of bleeding in non-MHV patients with warfarin treatment (15). Many risk factors for bleeding occur concomitantly with risk factors that are believed to increase the risk of TE, which further aggravates decision on target INR. Risk factors of major bleeding in MHV patients seem to share the same risk factors as other indications for warfarin therapy (16).

Many of the independent risk factors for mortality in our cohort have been reported in other studies with MHV (17-19). The low life expectancy and poor prognosis in many conditions as diabetes, liver -, kidney- and heart failure in the general patient, appear to be as vital in patients with MHV. Atrial fibrillation was in the present study surprisingly significant for mortality in spite of well-managed anticoagulation treatment. Atrial fibrillation and heart failure are conditions that share common risk factors and simultaneous presence of both conditions is common, especially in patients with preserved ejection fraction (20). The extraction of diagnoses in the Patient registry can imply risk of missing true diagnosis of heart failure with reduced ejection fraction, but above all heart failure with preserved ejection fraction. Since the risk of death in patients with heart failure with preserved ejection fraction is similar to patients with heart failure with reduced ejection fraction (21), there could be risk of confounding.

In order to obtain a more apparent perspective of the risk of stroke/TE in patients with AVR in different age spans, event rate was plotted against age. The event rate was fairly leveled between 40-70 years and increased significantly after 70 years of age. Similarly, the event rate of major bleeding was balanced at approximately 2.0 per 100 patient-years and increased substantially after 70 years of age. The risk of major bleeding was doubled compared to TE in patients with AVR, and nearly 2.5-folded in patients with MVR or combined valve prosthesis. This may be attributable to the higher INR target ranges of the latter group. In addition, it should be noted that the aforementioned rates cover first event and does not include the total number of

events. Consequently, the rates are probably underestimating the true incidence of the events, particularly for major bleeding events. Risk of stroke/TE within different age spans in patients with MHV is sparse in the literature. Recently, Idrees et al. (22) reported in a large nationwide database a stroke risk of 1.4% per year after isolated AVR, which is very similar to the rate found in our cohort (1.3 per 100 patient-years). However, the valves in the study by Idrees et al. included both MHV and bioprostheses, and furthermore, the anticoagulation status of the patients were not reported.

Our study has several limitations. Since this is an observational cohort we could not adjust for clinical information and outcomes that was not registered. Furthermore, prescriptions of drugs such as aspirin and $P2Y_{12}$-inhibitors, were extracted six months before study start with no definite awareness of the duration and concomitant use of these agents with warfarin when the study period started. Hence, these variables were not included in the multivariate analysis. Long-term concomitant use of aspirin or other antiplatelet agents with warfarin is however rare in Sweden (11). Our mortality rates do not include perioperative mortality. Furthermore, there is a risk that primary endpoints such as major bleeding and stroke/TE-events escapes registration due to sudden death, since adjudication of events and cause of death were not validated. Another important consideration is that we could not within this study identify the different type and model of the MHV that were implanted. However, during the study period only bileaflet valves were implanted in Sweden. Yet, the size of the cohort reflecting the nationwide Auricula and SWEDEHEART data that represents a large proportion of the patients in Sweden gives substance and strengthens the results of the study.

Conclusion

This nationwide cohort study in patients with MHV in a high TTR setting, confirms the predictive ability of previous TE for new stroke/TE events, whereas atrial fibrillation and heart failure were not associated with increased risk. Further, the incidence of major bleeding events is more than doubled compared to TE in all valve groups.

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Conflict of interest: none

References

1. Hering D, Piper C, Bergemann R, Hillenbach C, Dahm M, Huth C, et al. Thromboembolic and bleeding complications following St. Jude Medical valve replacement: results of the German Experience With Low-Intensity Anticoagulation Study. Chest. 2005;127(1):53-9.
2. Torella M, Torella D, Chiodini P, Franciulli M, Romano G, De Santo L, et al. LOWERing the INtensity of oral anticoaGulant Therapy in patients with bileaflet mechanical aortic valve replacement: results from the "LOWERING-IT" Trial. Am Heart J. 2010;160(1):171-8.
3. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(22):e57-185.
4. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH, American College of Chest P. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e576S-600S.
5. Joint Task Force on the Management of Valvular Heart Disease of the European Society of C, European Association for Cardio-Thoracic S, Vahanian A, Alfieri O, Andreotti F, Antunes MJ, et al. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J. 2012;33(19):2451-96.
6. Horstkotte D, Scharf RE, Schultheiss HP. Intracardiac thrombosis: patient-related and device-related factors. J Heart Valve Dis. 1995;4(2):114-20.
7. Puskas J, Gerdisch M, Nichols D, Quinn R, Anderson C, Rhenman B, et al. Reduced anticoagulation after mechanical aortic valve replacement: interim results from the prospective randomized on-X valve anticoagulation clinical trial randomized Food and Drug Administration investigational device exemption trial. J Thorac Cardiovasc Surg. 2014;147(4):1202-10.
8. Koertke H, Zittermann A, Wagner O, Ennker J, Saggau W, Sack FU, et al. Efficacy and safety of very low-dose self-management of oral anticoagulation in

patients with mechanical heart valve replacement. Ann Thorac Surg. 2010;90(5):1487-93.
9. Auricula. [Auricula årsrapport 2014], Auricula Annual Report 2014. UCR, Uppsala Clinical Research Center; 2015 [http://www.ucr.uu.se/auricula/index.php/arsrapporter/doc_download/53-auricula-arsrapport-2014. Accessed October 25, 2015]
10. Jernberg T, Attebring MF, Hambraeus K, Ivert T, James S, Jeppsson A, et al. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). Heart. 2010;96(20):1617-21.
11. Labaf A, Grzymala-Lubanski B, Stagmo M, Lovdahl S, Wieloch M, Sjalander A, et al. Thromboembolism, major bleeding and mortality in patients with mechanical heart valves- a population-based cohort study. Thromb Res. 2014;134(2):354-9.
12. Butchart EG, Payne N, Li HH, Buchan K, Mandana K, Grunkemeier GL. Better anticoagulation control improves survival after valve replacement. J Thorac Cardiovasc Surg. 2002;123(4):715-23.
13. Grzymala-Lubanski B, Labaf A, Englund E, Svensson PJ, Sjalander A. Mechanical heart valve prosthesis and warfarin - treatment quality and prognosis. Thromb Res. 2014;133(5):795-8.
14. Labaf A, Grzymala-Lubanski B, Sjalander A, Svensson PJ, Stagmo M. Glomerular filtration rate and association to stroke, major bleeding, and death in patients with mechanical heart valve prosthesis. Am Heart J. 2015;170(3):559-65.
15. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138(5):1093-100.
16. Fihn SD, McDonell M, Martin D, Henikoff J, Vermes D, Kent D, et al. Risk factors for complications of chronic anticoagulation. A multicenter study. Warfarin Optimized Outpatient Follow-up Study Group. Ann Intern Med. 1993;118(7):511-20.
17. Di Eusanio M, Fortuna D, De Palma R, Dell'Amore A, Lamarra M, Contini GA, et al. Aortic valve replacement: results and predictors of mortality from a contemporary series of 2256 patients. J Thorac Cardiovasc Surg. 2011;141(4):940-7.
18. Bouhout I, Stevens LM, Mazine A, Poirier N, Cartier R, Demers P, et al. Long-term outcomes after elective isolated mechanical aortic valve replacement in young adults. J Thorac Cardiovasc Surg. 2014;148(4):1341-6 e1.

19. Tjang YS, van Hees Y, Korfer R, Grobbee DE, van der Heijden GJ. Predictors of mortality after aortic valve replacement. Eur J Cardiothorac Surg. 2007;32(3):469-74.
20. Kotecha D, Piccini JP. Atrial fibrillation in heart failure: what should we do? Eur Heart J. 2015;36(46):3250-7.
21. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007;50(8):768-77.
22. Idrees JJ, Schiltz NK, Johnston DR, Mick S, Smedira NG, Sabik Iii JF, et al. Trends, Predictors, and Outcomes of Stroke After Surgical Aortic Valve Replacement in the United States. Ann Thorac Surg. 2016;101(3):927-35.

Table 1. Baseline preoperative characteristics.

	AVR	MVR	AVR/MVR
	Number of treatment periods		
	n=3751	n=866	n=193
Age	62.9 ±13.1	64.7 ±14.0	64.5 ±13.9
Female	1053 (28.1)	354 (40.9)	81 (42.0)
Time since valve replacement in years (IQR)	3.0 (IQR: 0-7.9)	4.1 (0.17-8.5)	4.2 (0-8.1)
	Treatment periods in patients with at least one diagnosis in the Patient register		
	n=3419	n=815	n=181
Hypertension	1009 (29.5)	212 (26.0)	60 (33.1)
Diabetes	353 (10.3)	89 (10.9)	35 (19.3)
Kidney failure	97 (2.8)	34 (4.2)	14 (7.7)
COPD	108 (3.2)	43 (5.3)	10 (5.5)
Liver failure	19 (0.6)	7 (0.9)	3 (1.7)
Atrial fibrillation	961 (28.1)	452 (55.5)	115 (63.5)
Heart failure	747 (21.8)	344 (42.2)	101 (55.8)
Vascular disease	223 (6.5)	87 (10.7)	20 (11.0)
PAH	31 (0.9)	30 (3.7)	8 (4.4)
Dyslipidemia	160 (4.7)	45 (5.5)	5 (2.8)
Alcohol consumption	58 (1.7)	15 (1.8)	3 (1.7)
Aspirin	594 (17.4)	92 (11.3)	28 (15.5)
$P2Y_{12}$ inhibitors	642 (18.8)	96 (11.8)	28 (15.5)
NSAID	154 (4.5)	35 (4.3)	3 (1.7)
SSRI	267 (7.8)	101 (12.4)	15 (8.3)
Endocarditis	269 (7.9)	128 (15.7)	29 (16.0)
Rheumatic heart disease	173 (5.1)	101 (12.4)	41 (22.7)
Previous Anemia	283 (8.3)	115 (14.1)	31 (17.1)
Previous stroke/TIA	384 (11.2)	111 (13.6)	27 (14.9)
Previous PCI	88 (2.6)	30 (3.7)	8 (4.4)
Previous ICH	78 (2.3)	25 (3.1)	7 (3.9)
Previous GI-bleeding	152 (4.4)	52 (6.4)	14 (7.7)
Previous other major bleeding	181 (5.3)	64 (7.9)	22 (12.2)
Concomitant CABG	709 (20.7)	200 (24.5)	33 (18.2)

Values are expressed as n (%) or means ± SD. Abbreviation: COPD, chronic obstructive pulmonary disease; PAH, pulmonary arterial hypertension; NSAID, non-steroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibitors; TIA, transient ischemic attack; PCI, percutaneous coronary intervention; ICH, intracranial hemorrhage; GI-bleeding, gastrointestinal bleeding; CABG, coronary artery bypass graft. Drugs prescriptions are six months before study start and not definite concomitant treatment.

Table 2. Rate of stroke/TE and major bleeding events.

	All patients n= 4,810	AVR n= 3,751	MVR n= 1,051
Stroke/TE	1.36 (1.20-1.54)	1.31 (1.13-1.50)	1.62 (1.20-2.14)
First major bleeding	2.91 (2.66-3.17)	2.64 (2.38-2.92)	3.93 (3.24-3.72) †
Intracranial	0.50 (0.41-0.62)	0.41 (0.32-0.53)	1.0 (0.68-1.41) †
Gastrointestinal	1.09 (0.94-1.25)	0.99 (0.84-1.16)	1.49 (1.09-1.99) ‡
Other	1.68 (1.50-1.88)	1.56 (1.36-1.77)	2.11 (1.62-2.70) ‡
Total major bleeding	3.20 (2.95-3.46)	2.89 (2.63-3.17)	4.49 (3.77-5.31) †

Rate is incidence per 100 patient-years (95% CI); AVR, aortic valve replacement; MVR, mitral valve replacement; † P <0.001; ‡ P <0.05.
Total major bleeding covers all subtypes of the major bleeding events, with only one event of each subtype permitted.

Table 3. Rate of stroke/TE and major bleeding events in relation to target INR.

AVR	Stroke/TE	Rate	Major bleeding	Rate
2.0-3.0	139	1.29 (1.09-1.52)	257	2.44 (2.15-2.76)
2.5-3.5; 2.0-4.0	27	1.20 (0.79-1.75)*	67	3.07 (2.38-3.90) †
MVR				
2.0-3.0	26	1,73 (1.14-2.51)	61	4.02 (3.07-5.16)
2.5-3.5; 2.0-4.0	8	1.77 (1.03-2.83)*	29	2.98 (1.99-4.28) ‡

Rate is incidence per 100 patient-years (95% CI); AVR, aortic valve replacement; MVR, mitral valve replacement; * not significant; † P =0.10; ‡ P =0.18.

Table 4. Risk factors of stroke/TE and major bleeding in patients with AVR.

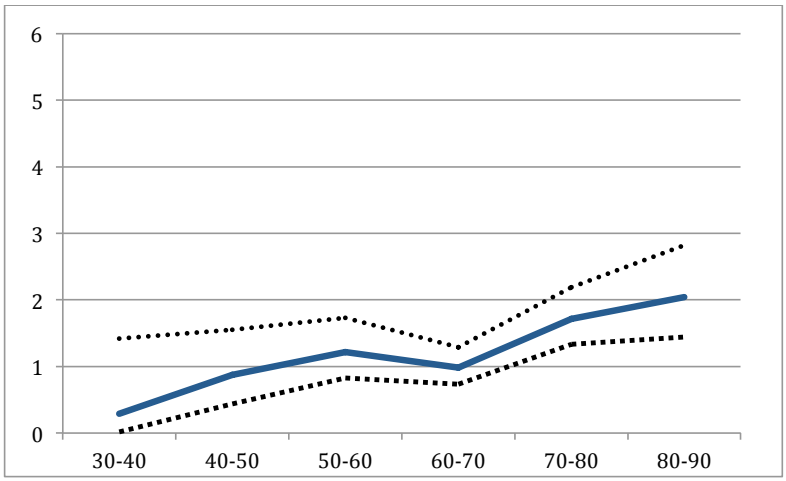
Stroke/TE	Univariate	P-value	Multivariate	P-value
Age	1.03 (1.01-1.04)	<0.001	1.02 (1.004-1.04)	0.012
Female	1.22 (0.88-1.69)	NS	1.03 (0.74-1.44)	NS
Kidney failure	0.88 (0.28-2.78)	NS	0.81 (0.25-2.56)	NS
Previous stroke	2.89 (1.95-4.00)	<0.001	2.44 (1.69-3.54)	<0.001
Diabetes	0.98 (0.57-1.66)	NS	0.83 (0.48-1.44)	NS
Hypertension	0.76 (0.54-1.06)	NS	1.18 (0.83-1.67)	NS
Atrial fibrillation	1.16 (0.82-1.64)	NS	1.0 (0.69-1.44)	NS
Heart failure	1.04 (0.71-1.52)	NS	0.90 (0.60-1.35)	NS
Vascular disease	1.79 (1.05-3.05)	0.03	1.64 (0.95-2.84)	0.075
Major bleeding				
Age	1.02 (1.02-1.03)	<0.001	1.02 (1.01-1.03)	<0.001
Female	1.27 (1.02-1.60)	0.035	1.14 (0.90-1.43)	NS
Hypertension	1.20 (0.95-1.52)	NS	1.03 (0.81-1.32)	NS
Kidney failure	2.23 (1.30-3.80)	0.003	1.71 (0.98-2.97)	0.057
Previous stroke	1.10 (0.79-1.55)	NS	0.89 (0.64-1.26)	NS
Liver failure	1.30 (0.32-5.20)	NS	1.35 (0.33-5.49)	NS
Alcohol overconsumption	2.05 (1.09-3.84)	0.025	1.81 (0.96-3.41)	0.069
Previous bleeding	2.85 (2.22-3.67)	<0.001	2.49 (1.91-3.25)	<0.001

HR, hazard ratio; CI, confidence interval; other abbreviations as table 1.
Multivariate analysis adjusted for the variables listed for each event and time since start of study period.

Appendix.

Condition	ICD-10 code, ATC code or Swedish procedure code beginning with
Preoperative characteristics	
Diabetes	E10-14
Hypertension	I10-15
Heart failure	I50, I110, I130, I132
Atrial fibrillation	I48
Stroke/TIA	I63-64, G45, I74, I693
Liver dysfunction	K70-77, JJC, JJB
Kidney disease	I120, I131-132, N17-19, DR016, DR024, KAS00, KAS10, KAS20
COPD	J43-44
Vascular disease	I21-I22, I252, I70-71
PAH	I27, P29.3B
Dyslipidemia	E780-782
Alcohol overconsumption	F10, K70, T51, Y90-91, E244, G312, G621, G721, I426, K292, K860, O354, Z714
Endocarditis	I330, I339, I389, I3898, B376
Rheumatic heart disease	I050-51, I060-62, I068-69
Previous anemia	D50, D510, D513, D518-19, D52-53, D55, D560-62, D568-72, D588-89, D60-64
Previous PCI	FNG05, FNG02, Z955
Previous ICH	I60-I62, S064-066, I690-92
Previous GI-bleeding	I983, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280,K282, K284, K286, K625, K920-922
Previous other major bleeding	D500, D508-509, D629, H365, H922, NO2, N938-939, R04, R310
Aspirin	B01AC06, B01AC56
Antiplatelet agents	BO1AC22, BO1AC24, B01AC04-05, B01AC07, B01AC30
SSRI	N06AB
Endpoint definitions	
Bleeding	
Intracranial	I60-I62, S064-066
Gastrointestinal	I983, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280,K282, K284, K286, K625, K920-922
Other	D500, D508-509, D629, H365, H922, NO2, N938-939, R04, R310
Thrombosis	
Stroke/TE/TIA	I63-64, I74, G45

Figure 1a. Rate of stroke/TE per 100 treatment-years in patients with AVR in relation to age categories of 10 years. Blue line (event rate) and dotted lines (95% CI).



1b. Rate of major bleeding events per 100 treatment-years in patients with AVR in relation to age categories of 10 years. Red line (event rate) and dotted lines (95% CI).

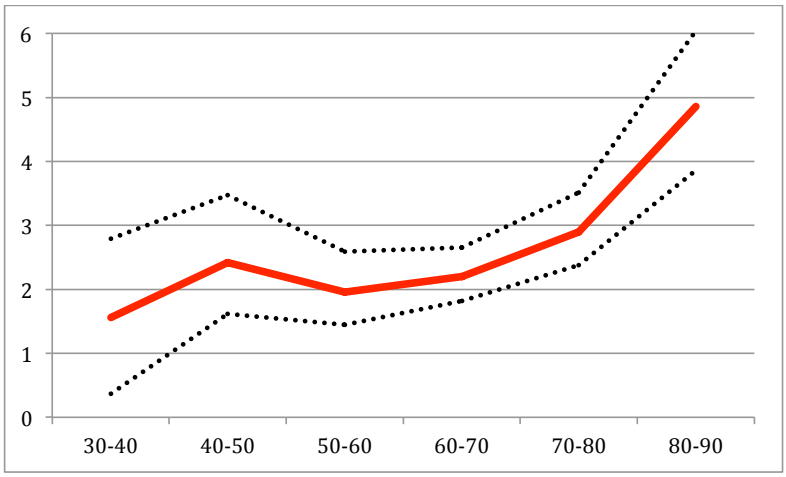


Figure 2a. Rate of stroke/TE per treatment years in patients with MVR and combined AVR/MVR in relation to age categories of 10 years. Blue line (event rate) and dotted lines (95% CI).

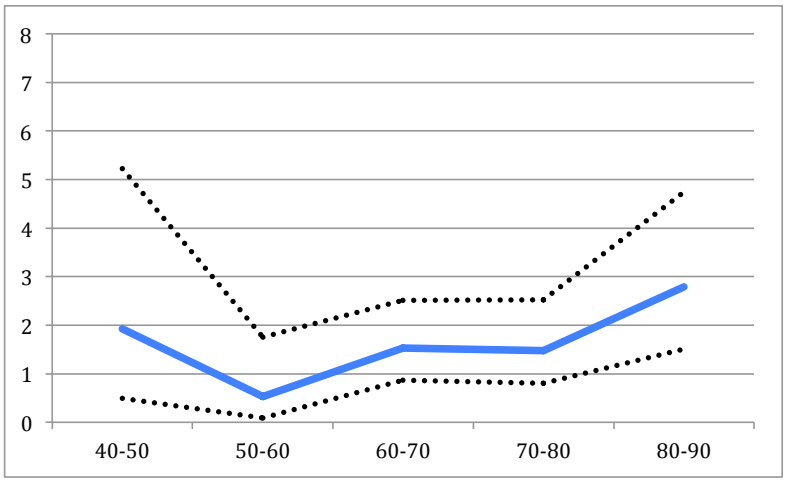
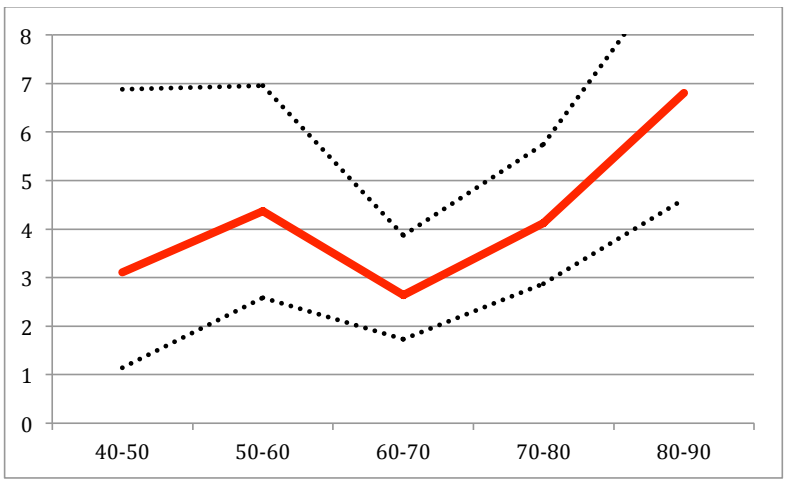


Figure 2b. Rate of major bleeding per treatment years in patients with MVR and combined AVR/MVR in relation to age categories of 10 years. Red line (event rate) and dotted lines (95% CI).



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