Anticoagulation treatment in patients with a mechanical heart valve

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ORIGIONAL PAPERS


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ABSTRACT

Background

Every year about 2,500 patients in Sweden undergo surgery for heart valve disease, primarily in the aortic valve. In contrast to the mitral valve, which can be repaired in 70% of the cases, the aortic valve is normally replaced by a mechanical or biological prosthesis. A mechanical heart valve (MHV) necessitates lifelong anticoagulation treatment with a vitamin K antagonist, most commonly warfarin, due to the high thrombogenicity of the prosthesis. The quality of the warfarin treatment is crucial in these patients. Compared to other countries, treatment quality in Sweden is very high; nonetheless, there is always room for improvement. One of the ways to achieve this improvement is to implement computerized dosing assistance. Treatment recommendations for anticoagulation intensity are based on few and old studies, making these recommendations uncertain. There is therefore a need for studies designed to establish the appropriate level of anticoagulation therapy.

Aim

The aim of these studies was to investigate the efficacy and safety of anticoagulation treatment among patients with mechanical heart valve prostheses in Sweden; to assess whether computerized dosing can increase the treatment quality; to investigate the influence of the treatment quality, measured by Time in Therapeutic Range (TTR) and INR variability, on the risk of complications and, finally, to establish the optimal intensity of anticoagulation treatment in this group of patients.

Methods

Data were obtained from AuriculA – a national quality registry established in 2006, which currently includes approximately 50% of all patients treated with oral anticoagulation in Sweden.

Study II used only data from AuriculA. 769,933 warfarin-dosing suggestions proposed by the dosing algorithm in AuriculA were analysed. Accepted dose suggestions (590,939) were compared with 178,994 manually-changed doses in regard to the resultant INR value,
measured as mean error (deviation from target INR) and hit rate (number of INR samples within the target range 2-3).

In study III, AuriculaA was used to identify patients in Sundsvall and Malmö in the period 2008 – 2011 who were receiving warfarin for a mechanical heart valve prosthesis, as well as to retrieve their INR data. Data on background characteristics and bleedings or thromboembolic complications were manually retrieved from medical records by two investigators. A total of 534 patients with mechanical heart valve prostheses were divided into quartiles based on TTR and were compared regarding the risk of complications. For Studies I and IV, data from AuriculaA were merged with the Swedish National Patient Register, SWEDHEART/ Heart surgery, and the Swedish Cause of Death Register, comprising in total 77,423 patients on warfarin with 217,804 treatment years. Every treatment period registered in AuriculaA was given an individual identification number. During the study period a patient could have any number of treatment periods. The number of complications in total and in different patient groups within the study population was investigated. Complications were defined by ICD-10 codes. Major bleeding was defined as an event necessitating hospital treatment and given a discharge diagnosis with one of the ICD-10 codes reflecting bleeding, as listed in the Appendix. Bleeding events were divided into intracranial, gastrointestinal and other bleedings. Thromboembolic complications consist of venous events (deep vein thrombosis, pulmonary embolism, venous stroke) or arterial events (stroke, TIA, acute myocardial infarction, peripheral arterial embolism).

Data were analysed using both simple, descriptive statistical methods and various tests such as Mann-Whitney (or two sample Wilcoxon), T-test, Chi 2 test, ANOVA, multivariate analysis with logistic regression and survival analysis with Cox Regression with proportional hazard assumption.

**Results**

**Treatment quality**

Mean TTR among all patients in Study I was 76.5% whereas patients with mechanical heart valve prostheses had a TTR of 74.5%. The annual incidence of major bleeding or thromboembolic events among all patients was 2.24% and 2.65%, respectively. The incidence of intracranial bleeding was 0.37% per year in the general population and 0.51% among patients with mechanical heart valve prostheses, who also had a higher bleeding rate in total (3.37% per year).
Both the mean and median errors were smaller (0.44 vs. 0.48 and 0.3 vs. 0.4, respectively) and the hit rate was higher (0.72 vs. 0.67) when the dose suggested by the algorithm was accepted, compared to when it was manually changed.

**TTR**

In Study III there was no significant difference in the risk of thromboembolism regardless of TTR level. Risk of bleeding in quartiles I and II was more than two times higher than in the quartile with TTR >82.9.

In Study IV, lower TTR (≤70%) was associated with a significantly higher rate of complications when compared with TTR >70%. Bleeding risk was higher in the group with lower TTR (HR=2.43, CI 2.02-2.89, p<0.001). After dividing patients into TTR quartiles, the rate of complications in total was significantly higher in quartiles I to III compared with quartile IV, which had the highest TTR. Risk of thromboembolism, major bleeding and death was higher in the first and second quartile compared to the quartile with the highest TTR.

**INR variability**

Higher INR variability above mean (≥0.40) was related to a higher rate of complications compared with lower INR variability (<0.40) as shown in Study IV. Bleeding risk was higher in the group with INR variability ≥0.40 (HR = 2.15, CI 1.75-2.61, p<0.001).

Comparison of quartile IV, which had the lowest INR variability, with the other three revealed that quartiles I and II, which had the highest INR variability, had significantly worse outcomes for all complications except for thromboembolic events, plus also death in quartile II.

**TTR and INR variability combined**

High variability and low TTR combined was associated with a higher risk of bleedings (HR 2.50, CI 1.99-3.15), death (3.34, CI 2.62-4.27) and thrombosis (1.55, CI 1.21-1.99) compared to the best group.

**Level of anticoagulation**

Higher warfarin treatment intensity (mean INR 2.8-3.2 vs. 2.2-2.7) was associated with a higher rate of bleedings (HR 1.29, CI 1.06-1.58), death (1.73, CI 1.38-2.16) and complications in total (1.24, CI 1.06-1.41) after adjustment for MHV position, age and comorbidity.
Conclusion

Warfarin treatment quality is crucial for patients with mechanical heart valve prostheses. Computerized dosing assistance could help maintain high warfarin treatment quality. Well-managed treatment with TTR ≥70% and INR variability below mean <0.40 is associated with a lower risk of serious complications compared with a lower TTR and higher INR variability.

No benefit of higher warfarin treatment intensity was found for any valve type or position.
Populärvetenskaplig sammanfattning

Människohjärtat består av fyra delar: två förmak och två kammare mellan vilka det finns klaffar som förhindrar backflöde av blod. Klaffar finns också mellan den vänstra kammaren och stora kroppspulsådern, och mellan den högra kammaren och lungartären. De vanligaste klaffsjukdomarna är förträngning av aortaklaffen och att mitralklaffen inte sluter tätt.

Varje år opereras ca 2500 patienter i Sverige på grund av hjärtklaffsjukdom, mestadels i aortaklaffen. Aortaklaffen ersätts vanligtvis med en mekanisk eller biologisk protes, medan mitralklaffen i stället kan repareras i 70% av fallen. En mekanisk hjärtklaff (MHV) kräver livslång antikoagulation med en K-vitaminantagonist, vanligen warfarin, beroende på klaffprotesens höga tendens för att bilda blodproppar. Warfarinets behandlingskvalitet är avgörande för dessa patienter.


Syftet med denna avhandling var att undersöka effekt och säkerhet av antikoagulationsbehandling hos patienter med mekanisk hjärtklaffsprotes i Sverige. Dessutom att bedöma om datoriserat doseringsstöd kan förbättra behandlingskvaliteten. Syftet var också att undersöka påverkan av behandlingskvalitet, mätt med tid i terapeutiskt intervall (TTR) och INR variabilitet, avseende risk för komplikationer. Slutfnigen, att försöka uppskatta den optimala intensiteten av warfarinbehandling i denna grupp av patienter.

sjukhusvård. Blödningar delades in i intrakraniella, från magtarmkanalen och andra blödningar. Tromboemboliska komplikationer definierades som venösa (djup ventrombos, lungemboli, venös stroke) eller arteriella händelser (stroke, TIA, akut hjärtinfarkt, perifer arteriell embolii).

I studie I har vi studerat kvalitet av behandling med warfarin samt risk för behandlingskomplikationer hos alla patienter som var registrerade i Auricula under studieperioden. Behandlingskvaliteten visade sig vara hög jämfört med andra länder och risken för allvarliga komplikationer var låg.

Studie II var utformad för att undersöka effekten av ett datoriserat ordinationsstöd. Den visade att en doseringsalgoritm kan ge bättre träffsäkerhet avseende efterföljande PK(INR)-värden än manuellt ändrade doser.

Studie III och IV inkluderade bara patienter med mekaniska hjärtklaffproteser. Studie III gjordes på en mindre population från Sundsvall och Malmö (534 patienter) och studie IV på samtliga patienter med mekanisk hjärtklaffprotes registrerade i Auricula (4687 patienter). Behandling med warfarin kontrolleras med ett så kallat PK (INR) prov. Hos friska människor ligger PK (INR) på omkring 1.0 medan patienter med mekanisk klaff bör ha ett PK (INR) mellan 2.0 och 3.5 (beroende på klafftyp och placering, samt andra riskfaktorer). Två mått som används för att bedöma behandlingskvalitet på warfarin är: TTR (Time in Therapeutic Range), som tar hänsyn till den tid under vilken patienten har ett PK(INR) värde inom avsett område, och INR variabilitet som visar hur mycket PK(INR) värdena varierar över tid.

Båda studier visade att både TTR och INR variabilitet spelar stor roll för risk för komplikationer och att man bör eftersträva högsta möjliga TTR (70% eller högre) och samtidigt lägsta möjliga INR variabilitet (0.40 eller mindre) för att minimera komplikationsrisken.

I studie IV har vi även försökt att fastställa optimal nivå av warfarinbehandling hos patienter med klaffprotes i olika positioner. För närvarande rekommenderas det att patienter med mekanisk aortaklaff bör ha PK(INR) mellan 2.0 och 3.0, medan den med mitralis klaffprotes är mellan 2.5 och 3.5. Det visade sig att den högre behandlingsintensiteten var associerad med högre risk för komplikationer i form av blödningar, död och komplikationer totalt, medan risken för proppbildning inte var mindre.

Sammanfattningsvis är warfarinets behandlingskvalitet avgörande för patienter med mekanisk hjärtklaffprotes. Datoriserad doseringshjälp kan bidra till att upprätthålla en hög behandlingskvalitet.
Välskött behandling med TTR ≥70% och INR variabilitet under medelvärdet <0,40 är associerad med en lägre risk för allvarliga komplikationer jämfört med lägre TTR och högre INR variabilitet.

Högre warfarinbehandlingsintensitet är inte till fördel oavsett klaffprotesens typ och position.
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
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<tr>
<td>ADP</td>
<td>Adenosine diphosphate</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>AS</td>
<td>Aortic stenosis</td>
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<tr>
<td>AT</td>
<td>Antithrombin</td>
</tr>
<tr>
<td>BSA</td>
<td>Body surface area</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>INR</td>
<td>International Normalized Ratio</td>
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<tr>
<td>ISI</td>
<td>International Sensitivity Index</td>
</tr>
<tr>
<td>ISTH</td>
<td>International Society on Thrombosis and Haemostasis</td>
</tr>
<tr>
<td>LMWH</td>
<td>Low-molecular weight heparin</td>
</tr>
<tr>
<td>LV</td>
<td>Left ventricle</td>
</tr>
<tr>
<td>MHV</td>
<td>Mechanical heart valve prosthesis</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>MR</td>
<td>Mitral regurgitation</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NOAC</td>
<td>Novel (non-vitamin K antagonist) oral anticoagulants</td>
</tr>
<tr>
<td>PT</td>
<td>Prothrombin time</td>
</tr>
<tr>
<td>SWEDEHEART</td>
<td>Swedish Web-system for Enhancement and Development of Evidence-based care in HEART disease evaluated according to recommended therapies</td>
</tr>
<tr>
<td>TFPI</td>
<td>Tissue factor pathway inhibitor</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
</tr>
<tr>
<td>TTR</td>
<td>Time in Therapeutic Range</td>
</tr>
<tr>
<td>VHD</td>
<td>Valvular Heart Disease</td>
</tr>
<tr>
<td>VKA</td>
<td>Vitamin K antagonists</td>
</tr>
<tr>
<td>VKOR</td>
<td>Vitamin K epoxide reductase</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous Thromboembolism</td>
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<td>WHO</td>
<td>World Health Organization</td>
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</table>
INTRODUCTION

Valvular heart disease (VHD)

The average human heart beats between 2.5 and 3 billion times during its lifetime. During this time, its four valves must maintain unidirectional blood flow to optimise the heart’s efficiency and to provide oxygenated blood to the whole body.

Valvular heart disease is not as common as other heart diseases such as hypertension, heart failure or coronary artery sclerosis but it is still important and challenging.

Epidemiology

Historically, the most common aetiology of VHD was rheumatic fever. In Western countries, rheumatic heart valve disease has been replaced over the last decades by VHD of degenerative origin.

It is assumed that approximately 2.5% of the population has valvular heart disease [1] the prevalence of which is related to age (more than 13% aged over 75 years) and is predominantly due to degenerative aetiology [2].

Because of the rising life expectancy in Western countries, the number and percentage of patients with degenerative VHD will also presumably increase. Even though the occurrence of rheumatic fever is decreasing, it is still the second most frequent cause of valvular heart disease in Europe.

The third most common cause of valvular heart disease is infectious endocarditis, which can necessitate valve replacement both before and after antibiotic treatment if the valve is damaged. Moreover, 25% of patients with active endocarditis require valve replacement as part of curative treatment [3]. Other less frequent causes of VHD are inflammation, carcinoids, drugs or irradiation [4, 5].

The most common valve disease in Europe and North America is aortic stenosis (AS) [1, 2]. It occurs in 4-5% of people aged over 65, whereas underlying aortic sclerosis is present in 25% of patients over 65 years and almost half of those over 75 years [6, 7]. Of all the valve diseases, it is the most common indication for surgery.
Diagnosis

The most common method of detecting valvular heart disease in asymptomatic patients is detection of murmurs during a physical examination. The intensity of the murmur can also give a first indication of the severity of the disease. However, it is important to remember that in patients with heart failure, the murmur can be silent even in the presence of serious valve disease.

The golden standard in the investigation of VHD is echocardiography. It is indicated in all patients with a cardiac murmur, with the exception of some young patients with a trivial mid-systolic murmur (innocent murmur) [8,9]. Echocardiography can confirm the diagnosis and also permits assessment of disease severity, mechanism and consequences. It is also useful for identification of any accompanying lesions such as disease in another valve or ascending aorta abnormalities. Combining and checking the consistency of a number of indicators can quantify the severity of the disease (see the chapter below on echocardiography). It is also important to keep in mind potential errors in measurements [8-10]. Therefore, patients should be examined by a skilled echocardiography technician with experience in valvular heart disease. If transthoracic examination provides suboptimal imaging, transoesophageal examination may be useful. Echocardiography is also indicated in cases of suspected valve thrombosis, prosthetic valve dysfunction and endocarditis.

Other non-invasive investigations include stress echocardiography, fluoroscopy, radionuclide angiography, computed tomography (CT) and magnetic resonance imaging (MRI). Apart from CT and MRI, which are used to assess the dimensions of the thoracic aorta, the other methods are used rarely and their usefulness in the diagnosing process is questionable. With regard to invasive methods, in practice the only invasive investigation is coronary angiography, which is used to assess coronary arteries before planned surgery [8,9].

Aortic stenosis (AS)

As mentioned above AS is the most common valve disease in Europe and North America [1,2] and its prevalence is increasing, as the population gets older. Aortic sclerosis is present in more than 25% of patients over 65 years of age and in almost half of patients over 75 years of age, while AS occurs in 4-5% of those >65 years [5,6]. It is the most common indication for valve surgery.

The most common aetiology is degeneration and calcification of an anatomically normal tri-leaflet valve or bicuspid valve (80% of cases), followed by rheumatic disease. Of the valves
that require surgery, 50% are bicuspid, 30-40% tricuspid and <10% are unicusp[11]. Rare causes include familial hypercholesterolaemia, hyperuricaemia or lupus erythematosus. The pathophysiology of calcific, degenerative AS has, until recently, been considered to be a passive process. Recent data however have changed this completely; it is an active and complex process with underlying chronic inflammation, lipoprotein deposition, renin-angiotensin system activation, osteoblastic transformation of valvular interstitial cells and active calcification [12-16].

The normal aortic valve area is 3-4 cm² [17]. Once the valve is <1.5 cm² a gradient between the LV and aorta appears. When the area is <1.0 cm² (or 0.6 cm²/m² BSA) AS is considered to be severe. Stenosis develops gradually, and is more rapid in bicuspid valves due to their lower efficiency in distributing mechanical stress. Valve obstruction leads to pressure overload in the left ventricle, subsequently resulting in the development of concentric hypertrophy, which takes place at different rates.

Diagnosis is usually made after detection of a systolic murmur during routine examination or after an echocardiographic examination for another reason. AS is a progressive disease and symptoms present usually between the second and fourth decade if a rheumatic origin, between the fifth and sixth decade in the bicuspid valves, and in the seventh to eighth decade if a degenerative aetiology.

The most common symptoms are dyspnoea and fatigue. In severe AS, angina may also be present but is not pathognomonic for AS.

The basic tool for diagnosis and evaluation of aortic stenosis is echocardiography. Evaluation is mainly based on measurement of the maximum jet velocity, mean transaortic gradient and valve area by continuity equation. AS is defined as severe when the following criteria are met: aortic jet velocity >4m/s, mean gradient >40-50 mmHg and valve area <1.0 cm² [8,9].

Several modern prospective studies have evaluated the natural history of AS [6,18-23]. Valve area decreases on average by approximately 0.1 cm²/year, the gradient increases by 7 mmHg/year and the peak aortic jet increases by 0.25 m/s.

The image below illustrates an echocardiographic view of severe aortic stenosis. Image with permission from Echocardiography Department of Institute of Cardiology, Krakow
There is no established medical treatment for patients with AS. Several retrospective studies have shown promising data on the beneficial effects of statins on AS progression. However, the data are still conflicting, and two randomized trials have not been able to show that statins could stop progression or induce regression of valve disease [24,25].

Due to the lack of medical treatment, the treatment of choice in severe aortic stenosis is surgical aortic valve replacement. After successful surgery, long-term survival is comparable with that expected, and the quality of life is greatly improved [26]. Valve replacement has also shown to be cost effective for all age groups [27].

At the same time, it is important not to forget the risks associated with surgery. Operative mortality in isolated aortic valve replacement is between 2 and 5% in patients under 70 years and increases to 5-15% in older patients. If operation is combined with bypass surgery, mortality is between 5-7% [2,28-34].

Current European Society of Cardiology guidelines highly recommend early valve replacement soon after symptom onset in all patients with severe AS [8]. Asymptomatic patients present a more complicated picture requiring careful assessment of the risks versus benefits.
Mitral regurgitation (MR)
The second most common valve disease in hospitalized patients is mitral regurgitation (MR) [2] (also believed to be the most common in the general population [1]), which can be primary (caused by abnormalities of the mitral valve apparatus) or secondary.

Due to the decreasing prevalence of rheumatic fever, degenerative MR is nowadays the most common aetiology in Europe [2] followed by rheumatic fever and infectious endocarditis. Secondary MR can be caused by ischemic heart disease; by annular dilatation and papillary muscle displacement, and by systolic dysfunction of the left ventricle, which decreases the mitral valve closing force [35,36].

Due to incomplete valve closure and a pressure gradient between the left ventricle and left atrium, mitral valve insufficiency causes a backflow – systolic regurgitation of blood from the left ventricle to the left atrium.

Mitral regurgitation can be acute – resulting from papillary muscle chorda rupture, leaflet tear or perforation – and can cause acute haemodynamic instability. Chronic regurgitation results in LV volume overload and leads to LV remodelling and eccentric hypertrophy. The haemodynamic state can remain compensated for many years.

Severe acute MR usually presents with severe dyspnoea, acute pulmonary oedema or congestive heart failure. Patients with chronic mitral regurgitation may be symptom-free for many years and present late with dyspnoea and tiredness.

At physical examination of a patient with severe primary MR a (holo-) systolic high-pitched murmur can be heard, loudest at the apex. In secondary MR, the murmur is usually of low intensity [37].

As with other valve diseases, echocardiography is the cornerstone in MR diagnosis and assessment. Several methods can be used to determine the severity of MR. The easiest is colour-flow mapping, which measures the regurgitation jet and the regurgitant jet to left atrial ratio. MR is considered severe when the jet area is >10 cm² or >40% of the left atrial area.
The width of the vena contracta, the narrowest part of the jet, is another measure correlated with quantitative measurements of MR. A width <3 mm corresponds to trivial or mild MR, whereas a width >7mm corresponds to severe MR [38].

Some recent observational studies have greatly improved our knowledge of the natural history of chronic primary mitral regurgitation. [39-41]. The presence of severe MR and symptoms gives an excess mortality overall. Even asymptomatic patients who have advanced MR managed conservatively have a poor clinical outcome. Although medical treatment options are limited, they are still wider than for patients with aortic stenosis, for example. Acute MR can be treated with diuretics and nitrates. ACE-inhibitors and beta-blockers are prescribed to reverse LV remodelling in functional MR combined with heart failure and systolic dysfunction [42].

In regard to surgical treatment, the cornerstone is annuloplasty. This is based on the concept of reducing or remodelling the posterior annulus in order to restore an optimal surface of coaptation. This is achieved using rings of different sizes and shapes [43]. The current practice in experienced centres means up to 90% undergo valve repair [44], but in recent registries this applies to only around 50% of cases [2]. Even though there are no randomized studies comparing outcome it is accepted that valve repair, if possible, is better than valve replacement. Valve repair is associated with lower perioperative mortality 1-3% vs. 3-6%,
higher survival rate, better preservation of LV function and lower long-term morbidity (thromboembolism, endocarditis and need for reoperation) [45-49]. Regardless of the type of surgical treatment, it is only indicated in patients with severe MR. Those who definitely qualify for treatment are symptomatic patients with EF>30% and without contra-indications for operation. Surgery in asymptomatic patients is questionable, because randomized studies do not provide evidence for any course of action.

Other valve diseases include aortic insufficiency, mitral stenosis, tricuspid stenosis and regurgitation. These occur mostly in developing countries; their prevalence in Western Europe is low and still decreasing.

Echocardiography
Echocardiography (ultrasonocardiography – UKG, ultrasound of the heart, echocardiography) – a diagnostic imaging technique allowing the study of the structures of the heart and large blood vessels using ultrasound. It was originally developed in 1953 by the Swedish doctor Inge Edler in Malmö in cooperation with Hellmuth Hertz [50].

Echocardiography has been a milestone in the development of modern cardiology and is an efficient and irreplaceable tool, which allows effective management of cardiology patients. It is a technique that is highly dependent on the skills of the physician conducting the examination.

Ultrasound systems (echocardiography is an ultrasound examination) are equipped with a row of transducers with different characteristics. Those used in echo examination are phased-array transducers able to perform M-mode, two-dimensional (2D) (recently also three-dimensional (3D)) and Doppler imaging [51].

Echocardiographic examination is usually conducted on patients lying on their left side with their left hand under their head. In this position the heart lies closer to the chest wall, whereas raising the arm expands the space between the ribs. This makes placement of the ultrasound easier and improves ultrasound access. This position captures images from the parasternal and apical windows. Additionally, images can be captured sub- and suprasternally [52-53].

2D echocardiography provides live, high-resolution pictures of the heart and is the basis of the examination.

The views obtained with the above-mentioned windows are parasternal long- and short-axis views and apical four-, five-, three- and two-chamber views.
In the long-axis parasternal view we can see the right and left ventricle, left atrium, left ventricle outflow tract (LVOT) as well as the mitral and aortic valves. The short-axis view provides pictures of the right ventricle and atrium, left atrium, pulmonic vein and artery, and tricuspid, pulmonary and aortic valves [54].

The apical views consist of pictures of both atria and ventricles and aorta including aortic, mitral and tricuspid valves from different angles and in various configurations [54].

M-mode echocardiography came into use in clinical practice in the early 1960s. It has been the main method of echocardiographic examination for more than 20 years, and is now mostly replaced by 2D echocardiography. However, it is still an important part of the investigations providing useful information on the valves and heart valve movement (which is useful in evaluation of the ejection fraction (EF)).

Three-dimensional echocardiography was the next step in the evolution of echo examination. This technique allows more accurate assessment of left ventricular volumes, function and mass and can be compared in its accuracy to magnetic resonance imaging (MRI). It enables good assessment of valve morphology allowing visualisation and judgement of valve pathology before a decision is taken on surgical treatment [55]. 3D echo is currently somewhat limited, mainly because of technical capabilities. Technical advances in both software and hardware will probably enable three-dimensional echocardiography to become routine practice.

The most important aspect of echocardiographic examination in regard to heart valves is the option of performing a non-invasive haemodynamic assessment. This is possible because of Doppler modality and colour flow imaging.

The Doppler effect is the physical phenomenon of a change in sound frequency when the object (generating the sound) moves relative to the observer. When it moves towards the observer, the frequency increases, when moving away it decreases.

Several different Doppler imaging modalities are used in echocardiographic examination:

- continuous wave Doppler
- pulsed wave Doppler
- colour Doppler (based on pulsed wave Doppler).

Doppler imaging can be used in all views from all windows. The most important though are apical views.

As mentioned above there are two main types of valve malfunction: valve stenosis and valve insufficiency (which can co-exist).
In valvular insufficiency, the valvular orifice does not close completely in systole (mitral and tricuspid insufficiency) or diastole (aortic insufficiency). Consequently, some of the blood flows back to the originating heart chamber. This results in a progressive volume overload causing enlargement of those chambers.

The following methods can be used for haemodynamic study of valvular insufficiencies:
- volumetric method, determining the blood volume flowing backwards through the pathological valve
- PISA (proximal isovelocity surface area) method
- the pressure half-time (PHT) representing the lapse of time in which the peak pressure gradient between two communicating chambers decreases by 50%.

When assessing valvular stenosis, the estimation of pressure gradients is fundamental. Two different valvular pressure gradients must be taken into consideration:
- maximal gradient
- mean gradient.

After measuring the maximal gradient, Bernoulli’s formula can be used to calculate the maximal blood velocity through the valve.

**Mechanical heart valve prosthesis (MHV)**

Although heart valves were documented by Leonardo da Vinci more than 500 years ago, it is only since the 1960s that they have been available for replacement. Developments in this area of medicine have been rapid.

In the last 50 years, about 5 million prosthetic heart valves have been implanted worldwide, and more than 300,000 patients receive an MHV every year [56]. In Sweden alone 20,000 patients live with a mechanical heart valve and a further 2,600 heart valve operations are performed every year [57].

Mechanical prosthetic heart valves have been in use for more than 50 years. The first valve replacements took place in 1960 [58,59].

Mechanical heart valve prostheses have a similar structure and consist of three basic elements: the occluder, the housing and the sewing ring. The occluder is one or more solid mobile parts, which may be a ball (e.g. Starr-Edwards valves), a disc or a leaflet, which can be semi-circular or circular. The housing may be a cage or ring structure made of an alloy or graphite coated with pyrolitic carbon.
In regard to the flow pattern through the valve, mechanical prostheses can be divided into two groups – those with lateral flow (ball-cage valves) or with central flow (tilting disc and bi-leaflet valves). The working principle for all MHVs is the same, and is based on passive movement and closure, which depend on the blood flow and pressure gradients in the heart. To avoid thrombosis, most of the MHV prostheses have a very small (1-5%) degree of insufficiency built-in.

As mentioned above, there are three main types of MHV: caged-ball, single leaflet or tilting-disk and bi-leaflet valves [3]. Caged-ball valves were first introduced in 1960 (Starr-Edwards valve) and have been the standard for almost 20 years [4]. They have been implanted in more than 175,000 patients worldwide [60]. The free ball design was intended to prevent thrombus formation [5]. However, it generates a wake of stagnant blood, which probably contributes to the high risk of thromboembolism seen with this type of prostheses [6]. Other potential problems are poppet damage (cracks), paravalvular leaks and infective endocarditis [61,62]. Despite its disadvantages, this type of valve has been a “golden standard” for a long time and other valve types have been compared to it. The next step in valve development was the single leaflet and tilting disks, which allow central blood flow and are therefore less thrombogenic than caged-ball valves [3]. The most recent improvement is the St Jude Medical bi-leaflet valve introduced in 1977 (together with other valves modelled on it) – and is currently the most commonly used MHV [7]. Bi-leaflet valves provide symmetric, central blood flow without turbulence, which further reduces the risk of clot formation [3].

Complications and their management

Mechanical heart valve prostheses are very thrombogenic. This is due to the combined effect of several factors. Firstly, the presence of synthetic material, which can damage blood cells and initiate a coagulation cascade. Other problems with an MHV are an effective orifice area, which is smaller than in the native valve, a pressure gradient through the prosthesis, and non-laminar flow. These factors cause disturbances in the blood flow and can in themselves lead to activation of haemostasis, which increases in combination with the presence of the metal prosthesis.
Valve thrombosis

The risk of prosthetic valve thrombosis has previously been reported to be 0.1 – 5.7% per patient year [63,64]. The risk is significantly higher when the prosthesis is located in the mitral position [65]. It is very important to maintain adequate anticoagulant treatment. If a patient is treated adequately, the risk of valve thrombosis is nearly the same for patients with MHV and bioprostheses [66]. Moreover, adequate treatment results in a similar incidence of valve thrombosis regardless of the type of prosthesis (caged-ball – single, tilting, disk or bi-leaflet – tilting, disk) despite the fact that they differ significantly in their thrombogenicity [67]. Valve thrombosis usually causes acute dynamic deterioration requiring immediate treatment but can sometimes have a more sneaking onset with symptoms present over a longer period (weeks or even months). Diagnosis can be confirmed using echocardiography and heart catheterization. Preferred treatment of smaller clots (<5 mm) is oral anticoagulation [68], whereas bigger clots demand more aggressive treatment with fibrinolysis or valve replacement. Surgical intervention is associated with a 15% mortality risk [69-71], which can be substantially increased in emergency surgery on haemodynamically unstable patients [71,72]. The success rate for thrombolytic therapy is about 70%, whereas the mortality rate is between 9 and 10% [73-77], and it is more effective for aortic valve thrombosis and in patients who have had symptoms for less than 2 weeks.

Embolism

The risk of major thromboembolic complication (other than valve thrombosis) resulting in death or permanent brain damage is about 4% per year in the absence of antithrombotic therapy; 2% per year with antiplatelet therapy; and approximately 1% per year with warfarin treatment [59]. The majority of these embolisms occur as cerebrovascular events [64,78]. The risk is higher in mitral valve prostheses, valves of the caged-ball type, and in patients with more than one prosthetic valve [65,79]. Other factors that increase the risk of embolism include atrial fibrillation, decreased left ventricle function, and age over 70 years. The risk of embolism with bioprosthetic valves was comparable to that with mechanical valves and adequate warfarin treatment.
Haemolysis

Subclinical intravascular haemolysis (increased serum lactate dehydrogenase, decreased serum haptoglobin and reticulocytosis) is present in most patients with MHV. However, severe haemolytic anaemia is uncommon [80-82] and usually indicates paravalvular leakage. The risk of an increased incidence and severity of haemolysis is higher in patients with caged-ball valves and those with more than one prosthesis [83,84].

Anticoagulation

Patients with mechanical heart valve prostheses require life-long anticoagulant treatment (such a need in patients with bioprostheses is controversial, and is still a question for debate), which must be started immediately after surgery (possibly within 6 – 12 hours). At present the only option for these patients is vitamin K antagonists (VKA), primarily warfarin and, in some cases, low-molecular weight heparin (LMWH). The RE-ALIGN study attempted to introduce dabigatran in these patients [85]. The dosage of dabigatran was based on creatinine clearance. Patients with a clearance of 110ml/min or higher received 300 mg dabigatran twice daily; those with a clearance between 70 and 109 ml/min received 220 mg twice daily; and those with a clearance below 70 ml/min received 150 mg twice daily. However, the outcome for patients in the dabigatran group was far worse and the study has been terminated. The patients on dabigatran suffered from ischemic stroke, myocardial infarction and valve thrombosis (not complications in the warfarin group). The risk of death and bleeding was also significantly higher in the dabigatran group. Therefore, dabigatran (and other NOACs) are not indicated for patients with MHV prosthesis.

Initially, the efficacy of anticoagulant treatment was assessed using prothrombin time (PT). The biggest problem with this method was the variability of the sensitivity of the thromboplastin reagent used in different laboratories. In other words, the same sample tested in different laboratories (or at the same laboratory on different occasions) could give completely different results. Therefore, in the 1980s PT was standardized and is now presented as the international normalized ratio (INR) [86] after correction for the international sensitivity index (ISI) – a comparison of the responsiveness of each laboratory’s thromboplastin reagent to that of a reference established by WHO (World Health Organization) with ISI assigned arbitrarily to 1.0. The normal INR range is between 0.8 and 1.2. Prothrombin time can be extended by anticoagulation treatment, malnutrition, vitamin K deficiency and its intensified metabolism in disseminated intravascular coagulation during septicaemia.
Haemostasis
Blood occurrence outside of the blood vessel initiates a process of haemostasis in order to stop the bleeding. As long as blood vessels are not damaged, their endothelial cells prevent blood-clotting with the help of molecules similar to heparin and thrombomodulin and at the same time they inhibit platelet aggregation. When the endothelium is damaged, it stops production of inhibitors and starts producing the von Willebrand factor which begins the process of maintenance of haemostasis after injury.

Haemostasis can be divided into three steps:

1. Vascular spasm (vasoconstriction), reducing the amount of blood loss. Parallel, the exposed collagen initiates platelet adhesion. Platelets release cytoplasmic granules containing serotonin, ADP and thromboxane A2, which increase the vasoconstriction effect. This step is most effective in smaller blood vessels [87,88].

2. Platelet plug formation. This process is activated by the von Willebrand factor (vWF) produced by damaged endothelium cells. In contact with damaged endothelium platelets activate and start connecting with each other and producing chemical molecules which activate even more platelets and increase vascular spasm. The formation of a platelet clot is known as primary haemostasis.

There are a dozen so-called coagulation factors circulating inactive in blood. Once activated they start to create the clot with help of a fibrin net which allows to keep the platelet plug in place. This net also binds red and white blood cells, which further consolidates the clot. This is known as secondary haemostasis.

3. Blood coagulation. The third and final step of haemostasis is the reinforcement of the platelet plug. With help of fibrin platelets come together forming a clot allowing platelets and other blood cells to stay in the injured area. At the same time changes it’s state from liquid to gel.

The coagulation cascade
There are two paths of activation of coagulation: intrinsic and extrinsic.
The intrinsic path is initiated by activation of factor XII after contact with collagen exposed in the damaged vessel wall. This then activates factor XI. The extrinsic path is activated through Tissue Factor (TF) released from endothelium cells. This is bound with factor VIIa to form complex TF-VIIa, the main functions of which are the conversion of factor X into Xa and factor IX into IXa. These, together with the cofactor, factor Va, activate the transformation of prothrombin into thrombin.
## Coagulation factors

<table>
<thead>
<tr>
<th>Number and/or name</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (fibrinogen)</td>
<td>Forms clot (fibrin)</td>
</tr>
<tr>
<td>III (tissue factor or tissue thromboplastin)</td>
<td>Co-factor of VIIa (formerly known as factor III)</td>
</tr>
<tr>
<td>IV Calcium</td>
<td>Necessary for coagulation factors to bind to phospholipid (formerly known as factor IV)</td>
</tr>
<tr>
<td>V (proaccelerin, labile factor)</td>
<td>Co-factor of X with which it forms the prothrombinase complex</td>
</tr>
<tr>
<td>VI</td>
<td><em>Unassigned</em> – old name of Factor Va</td>
</tr>
<tr>
<td>VII (stable factor, proconvertin)</td>
<td>Activates IX, X</td>
</tr>
<tr>
<td>VIII (Antihemophilic factor A)</td>
<td>Co-factor of IX with which it forms the tenase complex</td>
</tr>
<tr>
<td>IX (Antihemophilic factor B or Christmas factor)</td>
<td>Activates X: forms the tenase complex with factor VIII</td>
</tr>
<tr>
<td>X (Stuart-Prower factor)</td>
<td>Activates II: forms the prothrombinase complex with factor V</td>
</tr>
<tr>
<td>XI (plasma thromboplastin antecedent)</td>
<td>Activates IX</td>
</tr>
<tr>
<td>XII (Hageman factor)</td>
<td>Activates factor XI, VII and prekallikrein</td>
</tr>
<tr>
<td>XIII (fibrin-stabilizing factor)</td>
<td>Crosslinks fibrin</td>
</tr>
</tbody>
</table>
**Anticoagulation**

To maintain blood flow, it is important that the coagulation cascade is controlled through regulating factors. There are five control mechanisms:

- **Protein C** – a major physiological anticoagulant, dependent on vitamin K
- **Antithrombin (AT)**
- **Tissue Factor Pathway Inhibitor (TFPI)**
- **Plasmin**
- **Prostacyclin.**

These factors inhibit the coagulation process at different levels, as shown in the diagram above.

In addition to natural anticoagulants, there are a number of drugs that prevent blood coagulation, the most common of these is warfarin – and is almost the only drug suitable for patients with mechanical heart valve prostheses.

**Warfarin**

The history of warfarin begins in the 1920s in North America with an epidemic of a cattle disease manifested by spontaneous bleeding. Some of the animals had died after castration or dehorning. Autopsies demonstrated that the cause of death was fatal bleeding.

In 1921, Canadian veterinary pathologist Frank Schofield determined the cause to be ingestion of hay made from spoiled sweet clover. Using tests on rabbits he determined that the spoiled sweet clover acted as a powerful anticoagulant [87]. In 1929 another veterinarian from North Dakota, Dr L M Roderick, showed that the bleeding was caused by a haemorrhagic factor that reduced the activity of prothrombin [88]. In parallel, Henrik Dam from Denmark discovered that vitamin K deficiency was the cause of a haemorrhagic disease in chickens [89]. These poultry also had a prothrombin deficiency just like the cattle in North America. Later it was demonstrated that other vitamin K-dependent factors (VII, IX and X) were also lacking. Nevertheless, it wasn’t until 1940 that Karl Link from the University of Wisconsin, together with his student Harold Campbell, discovered that the anticoagulant agent in sweet clover was 3,3’- methylenebis (4-hydroxycoumarin) [90]. It took almost a further 5 years to synthesize this agent, which was then named dicoumarol. Dicoumarol is a product of the fermentation of the plant molecule coumarin, which, as we now know is present in many plants.
Coumarin is responsible for the sweet smell of newly cut grass. To acquire anticoagulant properties, coumarin must be fermented by fungi; this explains the presence of dicoumarol in the spoiled sweet clover stalks that had been attacked by fungi in large silos. Further work by Link led to the synthesis of warfarin in 1948. The name is derived from the Wisconsin Alumni Research Foundation (WARF) and coumarin (–arin). It was initially approved as rat poison in 1952, and was considered to be toxic to humans until an unsuccessful suicide attempt in 1952 [91] proved otherwise. This resulted in its registration for use in humans in 1954. The 1960s saw the first reports that different patients have diverse responses to a fixed dose warfarin [92].

![Warfarin as a potent rat poison.](www.homehardware.ca)

Warfarin is sold in Sweden under the labels Waran® and Warfarin Orion®. It has until recently been the only oral anticoagulant available in Sweden. It acts by inhibition of the vitamin K epoxide reductase (VKOR) [93] and, in particular, the subunit VKORC1. VKOR is an enzyme that reduces oxidized vitamin K after its participation in the carboxylation of coagulation factors, mainly Factors II (prothrombin), VII, IX, X, protein C and protein S. Warfarin contains two isomers, where S-warfarin is five times more potent than the R-isomer in regard to the inhibition of vitamin K reduction. Metabolism of warfarin is executed mainly by the CYP2C9 system. Gene polymorphism in VKORC1 [94] which makes VKOR less
susceptible to inhibition by warfarin, and individual variation in induction of CYP2C9, means that the response to warfarin doses varies strongly between patients [95]. The dose response also varies greatly after exposure to disease-related and environmental factors such as treatment with other drugs, dietary vitamin K content, and alcohol consumption [96].

The effect of treatment with warfarin on blood coagulation is measured as an international normalized ratio (INR) using the prothrombin test [97]. Target INR (interval) depends mostly on the indication for anticoagulation treatment (may be affected by comorbidity). Due to the fact that synthesized vitamin K-dependent plasma coagulation factors have to be catabolized and replaced by insufficient molecules, warfarin’s antithrombotic effect is not apparent directly after intake. Even though an early INR increase is noticeable due to the decrease in Factor VII, which has a short half-life, the full anticoagulant effect is present only after three to five days after there is a significant reduction in carboxylated Factor II, which has a longer half-life.

At the same time, warfarin also reduces protein C levels during the first 36 hours of treatment which, combined with the reduction of protein S, shifts the haemostatic system toward a prothrombotic state. Thus, to provide full protection against thrombus formation, treatment with warfarin can be initiated in combination with a more rapidly-acting anticoagulant such as heparin or low-molecular weight heparin (LMWH) [98].

On the other hand, because insufficiently carboxylated thrombin has a long half-life, warfarin treatment must be stopped a couple of days before any planned surgical intervention in order to allow the liver to refill the normal vitamin K-dependent factors. If bleeding occurs, the warfarin treatment must be immediately stopped and, depending on the severity, vitamin K or a concentrate of vitamin K-dependent coagulation factors (i.e. prothrombin complex concentrates, PCC) can be administered to support thrombus formation.

**TTR**

Quality of treatment with warfarin can be measured using different direct and indirect methods. Direct methods take into account the number of complications, which occur during treatment. One of the indirect methods is Time in Treatment Range. This is the percentage of time within the target range for each patient, calculated assuming a linear increase or decrease between two consecutive INR determinations according to Roosendaal’s method of linear interpolation [99]. A large meta-analysis of 47 studies of patients with atrial fibrillation
treated with warfarin reported that TTR and percentage of INR values in the therapeutic range were the most frequently used methods to determine the effectiveness of oral anticoagulation [100]. Because TTR also takes into account the time, it has been shown to be the better of these two methods and is considered to be the optimal measure of the quality of treatment with warfarin. It is currently used as the benchmark for assessment of treatment quality.

**INR variability**
Although TTR has proven to be a good indirect control of treatment quality it is still not perfect. It estimates the time spent within the target range using Rosendaal’s method [99] but does not take into consideration variation of the INR values within the target range. Fihn has described the variance growth rate [101] taking into account the time-weighted variance of the INR around the target INR, and reflecting the extent to which an actually achieved INR differs from the patient’s target INR during the time period. Since then both Fihn et al. [102] and Cannegieter et al. [103] have developed the formula in a way that considers the INR variance only, and does not refer to the target INR. If we say that TTR estimates the intensity of anticoagulation, INR variability reflects its stability and variance (fluctuation). In several studies on patients with atrial fibrillation, INR variability has been shown to be a predictor of thrombotic and bleeding events [101,104]. In another study, INR variability was an independent (from TTR) predictor of adverse events in patients with atrial fibrillation [105]. Only a few studies have been performed on these two measurements simultaneously, and only one involved patients with MHV prostheses [106]. This study has shown that the strategy involving both INR variability and Time in Therapeutic Range was better in regards to predicting complications compared with variability alone.

**Target INR**
Target INR in patients with mechanical heart valve prostheses has generally been poorly studied. Patients with aortic prostheses have in general a target INR of 2.5 (range 2.0-3.0). Higher target levels are recommended for patients with a prosthesis in a mitral position (target INR 3.0, range 2.5-3.5) or older types of prosthetic valves (here target INR can be up to 4.0, range 3.5 to 4.5 in patients with the Starr-Edwards caged-ball valve, and who have additional risk factors). There is a lack of recent, well-performed studies on these patients, and this deficit in the literature has resulted in differences in guidelines for these patients [8,9]. For example, the guidelines from the European Society of Cardiology restrict the addition of aspirin (to the vitamin K antagonist) only to patients with co-existing atherosclerosis or/and
recurrent thromboembolism despite oral anticoagulation [8] whereas ACC/AHA Guidelines recommend the combined therapy for all patients with mechanical heart valve prostheses [9]. Adequate anticoagulant treatment is an important issue. On the one hand, INR must be high enough to prevent thromboembolic events and, on the other, as low as possible to avoid bleeding complications, above all intracranial bleedings.
AIMS
The overall aim of this thesis was to study the efficacy and safety of anticoagulant therapy in patients with mechanical heart valve prostheses in Sweden. The aims of the specific studies were:

- To investigate the quality of warfarin treatment using the Swedish quality registry AuriculA (Study I)

- To study the impact of computerized dosing assistance on the quality of warfarin treatment (Study II)

- To elucidate the impact of the quality of warfarin treatment as measured by Time in Therapeutic Range (TTR) and INR variability in patients with mechanical heart valve prostheses (Studies III and IV).

- To investigate the optimal warfarin treatment intensity in patients with mechanical heart valve prostheses (Study IV).
METHODS

Patient data
Data for the studies were obtained from AuriculA, The Swedish National Patient Register, Cause of Death Register and SWEDHEART/Heart Surgery. We have also used information from patient medical records. The Table below presents the source of data for each study.

<table>
<thead>
<tr>
<th>Study</th>
<th>Source of data</th>
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<tbody>
<tr>
<td>Study I</td>
<td>AuriculA</td>
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<td></td>
<td>The Swedish National Patient Register</td>
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<tr>
<td>Study II</td>
<td>AuriculA</td>
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<tr>
<td>Study III</td>
<td>AuriculA</td>
</tr>
<tr>
<td></td>
<td>Medical records from hospital and primary care</td>
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<tr>
<td>Study IV</td>
<td>AuriculA</td>
</tr>
<tr>
<td></td>
<td>The Swedish National Patient Register</td>
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<td></td>
<td>Cause of Death Register</td>
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<td></td>
<td>SWEDHEART/Heart surgery</td>
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</tbody>
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Registries:

AuriculA

AuriculA is a national quality register for patients with atrial fibrillation who are treated with anticoagulation therapy. At the same time, it is a web-based dosing tool for warfarin. It is financed by the Swedish Association of Local Authorities and Regions (SKL). Started in 2006, it now includes over 125,000 patients (45-50% of all patients treated with anticoagulation (mainly warfarin) [107]), with over seven million INR values. More than 200 centres (primary healthcare centres as well as hospitals and specialist clinics) are affiliated to AuriculA and use it for administration of warfarin and NOACs. The most common indication
for oral anticoagulation is atrial fibrillation (70%), followed by venous thromboembolism (20%) and heart valve indication, mostly mechanical valves (10%).

AuriculA contains a warfarin dosing algorithm that generates a dose recommendation dependent on the patient taking the INR sample at the scheduled time, a target INR of 2.5 (range 2-3) and the current INR sample is not too different from the previous ones.

The algorithm core is based on 720 rules. Rules 1-72 are based on two previous INR values, and the following 648 rules on three previous INR values. Every rule consists of a narrow INR interval (0.1-0.2 in INR units) for the two (or three) previous values, and a dose suggestion. The algorithm can suggest manual prescription or a percentage change of the last dose. This can be an increase or decrease of 5%, 10% or 15%. It can also suggest continuing at the same dose (0% change).

Although healthcare services are well-aware of the risks associated with anticoagulation treatment, more and more reports are appearing of patients who have received life-threatening doses. Therefore, there is a need for a structured and strict control of treatment.

AuriculA has provided mainly demographic and INR data.

**The Swedish National Patient Register**

The Swedish National Patient Register provides data on diagnoses of patients discharged from hospitals since 1987, and on diagnoses from specialist clinics since 2001. ICD-10 classification has been used since 1997. Primary care diagnoses are not registered. The register has a very high validity, and information about primary diagnosis at discharge is lacking in only 0.5–0.9% of cases [108].

We have used the registry data on discharge diagnosis to identify complications and to establish the patient’s medical background (comorbidity).

**Cause of death register**

The Cause of Death Register was established in 1961 and contains data on the primary cause of death, date of death and contributing causes of death. Until 2011, it only contained data on registered permanent residents (regardless of whether they died in Sweden or abroad). Since 2012, it has covered all deaths in Sweden even if person was not registered as a permanent resident at the time of death. It has provided data on date of death in our study patients.
SWEDHEART/Heart surgery

SWEDHEART/Swedish Heart Surgery Register is a national quality register containing data on all heart valves implanted in Sweden since 1992 and includes details such as valve type, size and position. The register has very high validity, covering 98-100% of all open-heart surgery performed in Sweden. It has provided data on valve location and implantation date.

Study design

Study I

The aim of Study I was to investigate the risk of bleeding and thromboembolic complications in patients treated with warfarin in a large, unselected cohort with well-controlled treatment. We have included patients treated with warfarin who were registered in AuriculA between 1 January 2006 and 31 December 2011. By merging data from AuriculA with that from the National Patient Register we have achieved a study population of 77,423 unselected patients with 100,952 treatment periods and 217,804 treatment years. Every patient in our study could have one or more treatment periods. Every treatment period was assigned an individual identification number. For treatment exceeding the study period, start and end dates were set to the study’s start and end dates.

Complications were divided into thromboembolic complications and bleedings. Thromboembolic complications consist of (clinically verified) thromboembolic stroke/TIA, venous thromboembolism and myocardial infarction. Bleedings were divided in intracranial, gastrointestinal and other, and defined pursuant to the International Society of Thrombosis and Haemostasis with the exception of the criteria Hb reduction of 20g/L and transfusion of at least 2 blood units, as this data could not be obtained from the National Patient Registry. Diagnoses were extracted from the National Patient Register.

A list of ICD-10 codes defining all complications is presented below. Only primary diagnoses of cerebral bleeding or thromboembolic stroke and VTE were used in order to avoid over-registering. Similarly, we used a two-week “wash out” period for stroke and VTE to avoid double-reporting. This means that if a patient had been prescribed warfarin for stroke or VTE, it was not possible to register a new stroke or VTE in the first two weeks.
of treatment. Finally, in every treatment period only one complication of each type (subtype) was taken into account in the analysis. The patient’s age was always the age at the time that the complication occurred.

**Study II**

Study II aimed to investigate whether computerised dosing assistance can perform better than manual dosing. 53,779 patients treated with warfarin and registered in AuriculA between 1 January 2006 and 1 March 2011 were included. The only inclusion criterion was target INR of 2.5 (range 2-3). These patients had 1,061,529 INR values registered in AuriculA. We have excluded 228,868 because of missing values, caused mainly by an algorithm deficit. 62,278 INR values were excluded as the algorithm had initially suggested manual dosing. Consequently, 769,933 INR values were analysed of which 590,939 were algorithmic suggestions and 178,994 were manually-changed algorithmic suggestions.

We have investigated the algorithm’s performance for every rule and centre with two effect measures. We have compared the mean error and difference in hit rate between algorithmic suggestions and manual prescriptions. Mean error was defined as the distance from target INR (2.5), and hit rate was the number of INR values within target range (2-3).

Algorithm rules were divided into seven groups depending on the suggested dose change they provide: 0% (unchanged dose), ±5%, ±10% or ±15%. Another way of grouping is based on the number of previous INR values (two or three) on which the algorithm based the dose suggestion.

We have compared the mean error and hit rate between these seven rule groups and the number of previous values that suggestions were based on, both for accepted and manually changed suggestions.

**Study III**

The aim of Study III was to evaluate whether TTR impacts the risk of complications among patients with mechanical heart valve prostheses.

In this study, we have included all adult patients from Sundsvall and Malmö with mechanical heart valve prostheses registered in AuriculA between 1 January 2008 and 31 December
Two patients have been excluded – one with a tricuspid valve and one who declined to participate after receiving the information letter. Of the 543 patients left, nine more were excluded due to insufficient INR data, which made it impossible to calculate TTR. Analysis was finally performed on 534 patients (402 from Malmö and 132 from Sundsvall). Data on complications came from AuriculA, where they are registered continuously during every-day work with the system. These data were (simultaneously with data on comorbidity) confirmed by reviewing the patient’s medical records from specialist clinics: medicine, surgery, ophthalmology, laryngology, and gynaecology, as well as from primary care. Complications were divided into thromboembolic complications (valve thrombosis, stroke/TIA and other - among them myocardial infarctions), bleedings – according to the ISTH (International Society of Thrombosis and Haemostasis) definition (i.e. fatal bleeding, and/or equivalent blood loss greater than 20 g haemoglobin/L, requiring transfusion of at least 2 units of blood and/or bleeding that was verified by diagnostic radiology, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome) and death. We first investigated the relationship between the risk of these complications and TTR in the whole study group. Subsequently, patients were divided into quartiles in regard to their TTR (calculated according to Rosendaal’s method) and these groups were compared regarding the risk of complications (thromboembolic, bleedings and death).

**Study IV**

The purpose of Study IV was to evaluate the impact of TTR and INR variability (separately and combined) on the risk of serious complications (thromboembolic events, bleedings and death).

At the same time, we wanted to study whether the findings from Study III could be confirmed in a larger population. We also endeavoured to compare different INR target levels in regard to risks and benefits.

Data for our study were obtained by merging data from AuriculA, the Swedish National Patient Register, SWEDHEART/Heart surgery and the Swedish Cause of Death Register. The study was conducted on 3,831 patients with mechanical heart valve prosthesis registered in AuriculA between 1 January 2006 and 31 December 2011. These patients had 4,687 prescription periods and a total of 18,022 treatment-years on warfarin. We have excluded 10 patients with tricuspid valve prostheses and 134 patients for whom information on TTR was lacking.
Every patient could have one or more prescription periods during the study. For treatment periods exceeding the study period, the start and end dates were set to the study’s start and end dates.

Patients who had prostheses in both the mitral and aortic position were included in the mitral group.

Complications were defined in accordance with the same principle as that in Study II. Bleedings were divided into intracranial, gastrointestinal and other bleedings. Thromboembolic complications were venous (deep vein thrombosis, pulmonary embolism, venous stroke) or arterial (stroke, TIA, acute myocardial infarction, peripheral arterial embolism). The Complications list (ICD-10 codes) is the same for this study and Study I, and is presented below. Every patient could have any type of complication during the prescription period, but only one of each type was included in the analysis to avoid over-registration.

As in Study III, TTR was calculated in accordance with Rosendaal’s method and high TTR was defined as ≥70% in line with the current guidelines from the European Society of Cardiology. INR variability was estimated using Fihn’s method. In the absence of a previously established cut-off level, we have arbitrarily chosen a value of 0.40, which was the mean value in our population.

Patients were divided into four quartiles based on their individual TTR or INR variability. They were also divided into four groups (defined by both TTR and INR variability) from the best treatment quality (with TTR≥70% and INR variability ≤40) to the worst treatment quality (TTR <70% and INR variability >0.40). These groups were then compared in regard to the risk of complications.

All analyses compared (and TTR and INR variability were calculated for) prescription periods, not single patients.

Patients with mitral and aortic valve prostheses were divided into groups based on their target INR (2.5 and 3.0, ranges between 2.0 and 3.0 and between 2.5 and 3.5 respectively) and actual mean INR levels (ranges between 2.2 and 2.7 and between 2.8 and 3.3). These groups were also compared in regard to the risk of complications both unadjusted and after adjustment for age (patient’s age at the beginning of every prescription period), location of valve prosthesis, atrial fibrillation, heart failure, hypertension, diabetes and stroke.
List of ICD-10 codes defining underlying illnesses and complications.

<table>
<thead>
<tr>
<th>Condition</th>
<th>ICD-10 code or Swedish procedure code beginning with</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background characteristics:</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>E10–14</td>
</tr>
<tr>
<td>Hypertension</td>
<td>I10–15</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>I63–64, G45 (except G454), I69</td>
</tr>
<tr>
<td>Liver disease</td>
<td>K70–77, JJC, JJB</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>I120, I131-132, N17-19, DR016, DR024, KAS00, KAS10, KAS20</td>
</tr>
<tr>
<td>COPD</td>
<td>J43–44</td>
</tr>
<tr>
<td><strong>Endpoint definitions:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Bleeding:</strong></td>
<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td>I60–162, S064–066</td>
</tr>
<tr>
<td>Other</td>
<td>D500, D508–509, D629, H365, H922, N02, N938–939, R04, R310</td>
</tr>
<tr>
<td><strong>Thrombosis:</strong></td>
<td></td>
</tr>
<tr>
<td>Stroke/TE/TIA</td>
<td>I63–64, I74, G45 (except G454)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>I26, I636, I676, I80–82</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>I21–22</td>
</tr>
</tbody>
</table>

**Ethics**
Merging data from AuriculA, the National Patient Registry, the Cause of Death Registry and SWEDHEART/Heart Surgery as well as collecting data from patients’ medical records were approved by the Local Ethics Committee at Lund University and the Local Ethics Committee at Umeå University.
Patients registered in AuriculA were informed that their medical information would be registered in a national quality register. If they did not agree to registration of their data in the registry, their data was used only in the dosing program. After implantation of a heart valve prosthesis, patients are registered using online registration via the Internet. Databases are stored at Uppsala Clinical Research. They are then transferred to the National Board of Health and Welfare for interlinking with the Swedish National Patient Register and the Swedish Cause of Death Register. After this procedure, data was anonymised and could be used in our studies. It is not possible for researchers to identify any of the patients from the database. Consequently, there has been no contact between researcher and patient. This relates to Studies I, II and IV.

Study III had a different design. All patients were informed about the study by letter and asked for their permission to collect data. After entering the information from the patients’ medical records in the database, the data were anonymised and made unavailable for other studies. This means that only one person in Sundsvall and one in Malmö had access to personalized data. Moreover, the database was secured with a password.

Statistics

Study I

Data were analysed using descriptive analyses with SPSS Statistics (Version 21; SPSS Inc., IBM Corporation, NY, USA), and R version 3.0.0, R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/. Confidence intervals (CI) are 95%.

Study II

Using Mann-Whitney (or two-sample Wilcoxon) type tests we checked two measures for every centre and rule, respectively. These were the mean error (defined as distance from target INR) and hit rate, which was defined as the number of INR samples within the target range of 2.3. INR values were measured up to 1 decimal point. Centre TTR (cTTR) was compared to check if it was associated with how often each centre accepted/declined algorithm dose suggestions.
Study III

We first investigated the impact of TTR on the risk of bleeding, thrombosis or death in the whole study group using the T-test. The patients were then grouped into four quartiles based on their individual TTR: TTR <61.6, 61.6 to 71.9, 71.9 to 82.9 and >82.9%. Multivariate logistic regression was performed to compare the groups in regard to the risk of serious complications such as thromboembolism, bleeding or death per treatment year. A 95% confidence interval of person-time incidence rate with normal approximation was applied for rates of complications.

Data were analysed using SPSS Statistics (Version 21; SPSS Inc., IBM Corporation, NY, USA). A test with p-value less than 0.05 was considered statistically significant.

Study IV

Incidence rates per 100 patient-years were calculated using OpenEpi, version 3.03 (www.openepi.com). A 95% confidence interval of person-time incidence rate with normal approximation was calculated for rates of complications for all patients; for mitral and aortic valve prostheses separately; for patients with TTR <70% and those with TTR ≥70%; and finally, for patients with INR variability ≥0.4001 and those with ≤0.4000. Corresponding groups were compared regarding incidence rate of thromboembolism, bleeding and death per 100 treatment-years. Incidence rates where the 95% confidence intervals did not overlap were considered to vary significantly.

To investigate the risk of complications between different quartiles relative to TTR and INR variability separately and combined, we used survival analysis with Cox Regression and the best quartile as reference. The same analysis was performed on patients with different target and mean INR.

Data were analysed using SPSS Statistics (Version 22; SPSS Inc., IBM Corporation, NY, USA) and R version 3.0.0, R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/. A p-value less than 0.05 was considered statistically significant.
Statistical methods used in the studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Methodologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study I</td>
<td>Simple descriptive analyses</td>
</tr>
<tr>
<td>Study II</td>
<td>Mann-Whitney (or two-sample Wilcoxon)</td>
</tr>
</tbody>
</table>
| Study III | T-test  
Chi-squared test with and without linear-by-linear association  
ANOVA  
Multivariate analysis with logistic regression |
| Study IV | Simple descriptive analyses  
One-sample Kolomogorov-Smirnov test  
Survival analysis with Cox regression with proportional hazard assumption  
T-test |
RESULTS

**Patient's background**
Table 1 presents the background characteristics of patients as per the different studies.

**Table 1.** Background characteristics of patients included in all studies: number of patients, age, sex, comorbidity (hypertension, diabetes, previous stroke/TIA), TTR and mean INR.

<table>
<thead>
<tr>
<th></th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients n</strong></td>
<td>75,231</td>
<td>534</td>
<td>388</td>
<td>4687</td>
</tr>
<tr>
<td><strong>Mean age y (SD)</strong></td>
<td>70.2 (12.6)</td>
<td>65.4</td>
<td>65.4</td>
<td>63.3 (13.4)</td>
</tr>
<tr>
<td><strong>Women %</strong></td>
<td>40.6</td>
<td>38.0</td>
<td>31.4</td>
<td>56.2</td>
</tr>
<tr>
<td><strong>HT %</strong></td>
<td>47.8</td>
<td>63.9</td>
<td>63.9</td>
<td>63.7</td>
</tr>
<tr>
<td><strong>Diabetes %</strong></td>
<td>16.4</td>
<td>14.0</td>
<td>12.6</td>
<td>17.8</td>
</tr>
<tr>
<td><strong>Stroke/TIA %</strong></td>
<td>21.4</td>
<td>11.8</td>
<td>10.3</td>
<td>15.8</td>
</tr>
<tr>
<td><strong>TTR (SD)</strong></td>
<td>76.5 (17.8)</td>
<td>71.3 (14.54)</td>
<td>73.4 (14.6)</td>
<td>65.7 (29.1)</td>
</tr>
<tr>
<td><strong>Mean INR (SD)</strong></td>
<td>2.51</td>
<td>2.65 (0.43)</td>
<td>2.63 (0.43)</td>
<td>2.73 (0.45)</td>
</tr>
</tbody>
</table>

HT- hypertension, Ao - Aortic valve prosthesis, Mi - mitral valve prosthesis

**Study I**
77,423 unselected patients treated with warfarin were investigated. The most common treatment indications were AF, VTE, and heart valve disease. Table 2 presents baseline patient characteristics.

**Table 2.** Baseline patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Atrial fibrillation</th>
<th>Heart valve disease</th>
<th>Venous thromboembolism</th>
<th>Other indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of treatment periods on warfarin</strong></td>
<td>n=100,952</td>
<td>n=68,797</td>
<td>n=8,723</td>
<td>n=20,496</td>
<td>n=7,359</td>
</tr>
<tr>
<td><strong>Mean age</strong></td>
<td>69.8</td>
<td>72.1</td>
<td>66.1</td>
<td>65.3</td>
<td>66.2</td>
</tr>
<tr>
<td><strong>Women n (%)</strong></td>
<td>40,067 (39.7)</td>
<td>26,521 (38.5)</td>
<td>2,979 (34.1)</td>
<td>9,581 (46.7)</td>
<td>2,728 (37.0)</td>
</tr>
<tr>
<td><strong>Mean TTR %</strong></td>
<td>76.5</td>
<td>77.4</td>
<td>74.5</td>
<td>75.9</td>
<td>76.0</td>
</tr>
<tr>
<td><strong>Diabetes %</strong></td>
<td>17.1</td>
<td>18.8</td>
<td>14.0</td>
<td>12.3</td>
<td>18.6</td>
</tr>
<tr>
<td><strong>Hypertension %</strong></td>
<td>49.7</td>
<td>56.8</td>
<td>36.3</td>
<td>35.2</td>
<td>42.6</td>
</tr>
<tr>
<td><strong>Previous stroke/TIA %</strong></td>
<td>22.0</td>
<td>25.0</td>
<td>13.3</td>
<td>11.0</td>
<td>41.7</td>
</tr>
<tr>
<td><strong>Liver disease %</strong></td>
<td>1.1</td>
<td>0.9</td>
<td>0.8</td>
<td>1.6</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Kidney disease %</strong></td>
<td>3.9</td>
<td>3.8</td>
<td>3.9</td>
<td>4.2</td>
<td>4.9</td>
</tr>
<tr>
<td><strong>COPD %</strong></td>
<td>11.1</td>
<td>10.9</td>
<td>9.4</td>
<td>13.4</td>
<td>9.9</td>
</tr>
</tbody>
</table>
All patients studied gave a total of 217,804 treatment-years on warfarin. TTR (time in the INR range between 2.0 and 3.0 regardless of target INR) was high for all indications (Table 2).

The annual incidence of major bleedings and thromboembolic events was 2.24% and 2.65%, respectively (Table 3).

Table 3. Annual event rates in relation to gender and indication for warfarin treatment.

<table>
<thead>
<tr>
<th></th>
<th>Bleeding rate (% annually)</th>
<th>Thromboembolic rate (% annually)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>2.24 (2.21–2.27)</td>
<td>2.65 (2.62–2.69)</td>
</tr>
<tr>
<td>Men</td>
<td>2.16 (2.12–2.20)</td>
<td>2.69 (2.64–2.73)</td>
</tr>
<tr>
<td>Women</td>
<td>2.38 (2.33–2.44)</td>
<td>2.62 (2.56–2.67)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.18 (2.14–2.22)</td>
<td>2.65 (2.61–2.69)</td>
</tr>
<tr>
<td>Heart valve disease</td>
<td>3.37 (3.25–3.48)</td>
<td>2.57 (2.47–2.67)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>2.00 (1.93–2.07)</td>
<td>2.69 (2.60–2.77)</td>
</tr>
<tr>
<td>Other</td>
<td>2.18 (2.07–2.29)</td>
<td>3.53 (3.39–3.67)</td>
</tr>
</tbody>
</table>

Bleeding rate was highest among patients with heart valve disease at 3.37% whereas the highest rate of thromboembolic events of 3.53% was seen in patients with the indication “other”.

The mean per year incidence of intracranial bleeding was 0.37% in the whole population and 0.51% for patients with heart valve disease. These patients also had a higher risk of GI and other bleedings (1.11% and 1.83%, respectively) compared to patients with all other indications for warfarin treatment. Female gender was associated with a higher per year rate of major bleeding (2.38%, vs 2.16% in men), but at the same time was associated with a lower rate of intracranial bleeds (0.34% vs. 0.39% in men).

Bleeding and thromboembolic events were both positively correlated (except VTE) with age (Table 4). The annual bleeding rate for patients over 90 is higher than 4%. Figure 1 (Figure 1) presents the relationship between age and intracranial bleedings in patients with AF and an accumulated 142,626 treatment-years.
Table 4. Bleedings and thromboembolic events per treatment year versus age groups.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Bleeding</th>
<th></th>
<th></th>
<th>Thrombosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intrapulmonary</td>
<td>Gastrointestinal</td>
<td>Other</td>
<td>Stroke/TE/TIA</td>
<td>VTE</td>
</tr>
<tr>
<td>&lt;50</td>
<td>0.12</td>
<td>0.12</td>
<td>0.49</td>
<td>0.44</td>
<td>0.12</td>
</tr>
<tr>
<td>50–60</td>
<td>0.24</td>
<td>0.34</td>
<td>0.73</td>
<td>0.13</td>
<td>0.07</td>
</tr>
<tr>
<td>60–70</td>
<td>0.28</td>
<td>0.43</td>
<td>0.76</td>
<td>1.31</td>
<td>0.08</td>
</tr>
<tr>
<td>70–80</td>
<td>0.39</td>
<td>0.70</td>
<td>0.99</td>
<td>1.71</td>
<td>0.10</td>
</tr>
<tr>
<td>80–90</td>
<td>0.45</td>
<td>0.93</td>
<td>1.55</td>
<td>2.28</td>
<td>0.12</td>
</tr>
<tr>
<td>&gt;90</td>
<td>0.83</td>
<td>1.20</td>
<td>2.13</td>
<td>2.56</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 1. Risk of intracranial bleeding per treatment year related to age of patients with atrial fibrillation (n = 68,797).

Study II
53,779 patients with target INR 2.5 (range 2.0 – 3.0) from 125 participating centres were included. Mean TTR was 73%. 1,061,529 INR values were registered in AuriculA. 228,868 were excluded due to missing values. 67,728 INR values, which resulted in an algorithm
recommendation of manual change, have also been excluded. Of the remaining 769,933 values, 590,939 were prescribed in accordance with the algorithm suggestion and in 178, 994 the algorithm suggestion has been manually changed. Patients for whom algorithm suggestions were accepted had smaller mean and median errors and a higher hit rate compared with those for whom algorithm suggestions were manually changed (Table 5).

Table 5. INR values and their errors depending on the prescriber’s decision on algorithm suggestion.

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Mean error</th>
<th>Median error</th>
<th>Hit rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0.45</td>
<td>0.3</td>
<td>0.71</td>
</tr>
<tr>
<td>Algorithm based</td>
<td>0.44</td>
<td>0.3</td>
<td>0.72</td>
</tr>
<tr>
<td>Manually changed</td>
<td>0.48</td>
<td>0.4</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Algorithm rules can be grouped according to the change to the previous prescription suggested: 0% (unchanged weekly dose), ±5%, ±10% or ±15%. A second grouping is based on the number of previously measured INR values (two or three) on which the algorithm bases its dose suggestion. When three or more previous INR values were present, the accepted algorithmic dose suggestions were significantly better than those manually changed in most of the cases (except for the +15% category where the groups were equal). Figures 2 and 3 present how the mean error and hit rate change with the rule categories and the number of previous values available.
Figure 2. Mean error in INR values grouped according to rule category and the number of previous values on which the algorithm based its prescription.
Figure 3. Hit rate comparing accepted dose suggestions from the algorithm and those that were manually changed. Grouped according to rule category and the number of previous values on which the algorithm based its ordination.
Study III

All adult patients from Malmö and Sundsvall with mechanical heart valve prostheses who were registered in AuriculA between 1 January 2008 and 31 December 2011 were initially included. After excluding one patient with a tricuspid valve prosthesis, one who declined to participate, and nine other patients with insufficient INR data, 543 patients (132 from Sundsvall and 402 from Malmö) with a total of 1,814 patient-years on warfarin treatment were analysed.

Mean TTR was 71.3% (median 71.9%) for the whole group; 68.2% for women and 73.1% for men. 388 patients had a valve prosthesis in the aortic position, 119 in the mitral position and 26 had both aortic and mitral prostheses.

Patients were divided into four quartiles depending on their individual TTR.

Mean age varied significantly between the TTR quartiles (p = 0.033) although there was no apparent trend. The presence of other diseases and mean CHADS2 did not differ significantly between the TTR quartiles (Table 6).

Table 6. Comorbidity and age in relation to TTR (%) divided into quartiles.

<table>
<thead>
<tr>
<th></th>
<th>Quartile 4 (&gt;82.9)</th>
<th>Quartile 3 (82.9 – 71.9)</th>
<th>Quartile 2 (71.9 – 61.6)</th>
<th>Quartile 1 (&lt;61.6)</th>
<th>Sign.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years), mean (SD)</td>
<td>63.5 (12.1)</td>
<td>64.4 (14.8)</td>
<td>68.3 (13.3)</td>
<td>65.3 (15.4)</td>
<td>0.033</td>
</tr>
<tr>
<td>Comorbidity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF</td>
<td>47 (35.1)</td>
<td>47 (35.3)</td>
<td>57 (42.9)</td>
<td>57 (42.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14 (10.4)</td>
<td>16 (12.0)</td>
<td>24 (18.0)</td>
<td>21 (15.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>93 (69.4)</td>
<td>77 (57.9)</td>
<td>89 (66.9)</td>
<td>82 (61.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous Stroke/TIA</td>
<td>17 (12.7)</td>
<td>17 (12.8)</td>
<td>14 (10.5)</td>
<td>15 (11.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart failure</td>
<td>52 (38.8)</td>
<td>61 (45.9)</td>
<td>65 (48.9)</td>
<td>67 (50.0)</td>
<td>NS</td>
</tr>
<tr>
<td>CHADS2 mean (SD)</td>
<td>1.6 (1.3)</td>
<td>1.7 (1.4)</td>
<td>1.9 (1.4)</td>
<td>1.8 (1.4)</td>
<td>NS</td>
</tr>
</tbody>
</table>
57 patients experienced a thrombosis and 77 serious bleeding, and 85 patients died during the study period.

T-test performed on the whole study group (before dividing into quartiles) showed a difference in mean TTR between patients with and without a bleeding event (mean 67.7 vs 71.9, p=0.017), death (mean 66.6 vs 72.2, p=0.001) and all complications (68.3 vs 72.5, p=0.002) but not for thromboembolic events (69.4 vs 71.4).

The risk of serious complications was significantly higher with lower levels of TTR for all types of complications (p = 0.005), bleeding (p = 0.01) and death (p = 0.018) but not for thromboembolic events (Table 7).

**Table 7.** Complications at different levels of individual TTR divided into quartiles.

<table>
<thead>
<tr>
<th>TTR (%)</th>
<th>&gt;82.9</th>
<th>82.9 – 71.9</th>
<th>71.9 – 61.6</th>
<th>&lt;61.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>134</td>
<td>133</td>
<td>133</td>
<td>134</td>
</tr>
<tr>
<td>Time of treatment (y)</td>
<td>464.6</td>
<td>446.5</td>
<td>454.9</td>
<td>448.0</td>
</tr>
<tr>
<td>All complications n (rate)</td>
<td>27 (5.8)</td>
<td>43 (9.6)</td>
<td>40 (8.8)</td>
<td>50 (11.2)</td>
</tr>
<tr>
<td>Bleedings n (rate)</td>
<td>9 (1.9)</td>
<td>22 (4.9)</td>
<td>21 (4.6)</td>
<td>25 (5.6)</td>
</tr>
<tr>
<td>Thromboses n (rate)</td>
<td>9 (1.9)</td>
<td>16 (3.6)</td>
<td>18 (4.0)</td>
<td>14 (3.1)</td>
</tr>
<tr>
<td>Death n (rate)</td>
<td>16 (3.4)</td>
<td>17 (3.8)</td>
<td>23 (5.1)</td>
<td>29 (6.5)</td>
</tr>
</tbody>
</table>

Using multivariate analysis, the total number of complications was significantly higher in the first (p=0.011) and third (p=0.042) quartile compared to the fourth quartile with highest TTR. The risk of bleeding complications was significantly higher (p=0.022 and p=0.011) in the first and third quartile as compared with the best, whereas no impact of TTR on the risk of thromboembolic events was found (Table 8).
Table 8. Multivariate logistic regression, risk of complications due to TTR divided into quartiles.

<table>
<thead>
<tr>
<th>TTR (%)</th>
<th>&gt;82.9</th>
<th>82.9 – 71.9</th>
<th>71.9 – 61.6</th>
<th>&lt;61.6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compl. Total:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted OR</td>
<td>Ref</td>
<td>1.9, p=0.042</td>
<td>1.3, p=NS</td>
<td>2.1, p=0.011</td>
</tr>
<tr>
<td><strong>Bleedings:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted OR</td>
<td>Ref</td>
<td>2.6, p=0.022</td>
<td>2.2, p=NS</td>
<td>2.9, p=0.011</td>
</tr>
<tr>
<td><strong>Thromboses:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted OR</td>
<td>Ref</td>
<td>1.8, p=NS</td>
<td>1.7, p=NS</td>
<td>2.0, p=NS</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted OR</td>
<td>Ref</td>
<td>0.9, p=NS</td>
<td>0.9, p=NS</td>
<td>1.5, p=NS</td>
</tr>
</tbody>
</table>

Adjusted OR is adjusted for AF, Heart failure, Hypertension, Diabetes, Stroke, AMI and Age

Study IV

3,831 patients with 4,687 ordination periods (18,022 treatment years on warfarin) were investigated. 78% (3,656) had a prosthesis in the aortic position, 18% (842) in the mitral position and 4% (189) in both positions. Over 30% of all patients were women, and they comprised 40% of the patients with mitral valve prosthesis. Patient characteristics are presented in Table 9.

Table 9. Patient characteristics according to indication for warfarin

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Aortic valve</th>
<th>Mitral valve*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of treatment periods on warfarin</td>
<td>n=4,687</td>
<td>n=3,656</td>
<td>n=1,031</td>
</tr>
<tr>
<td>Mean age</td>
<td>63.26</td>
<td>62.91</td>
<td>64.51</td>
</tr>
<tr>
<td>Female sex n (%)</td>
<td>1,442 (30.8)</td>
<td>1,022 (28.0)</td>
<td>420 (40.7)</td>
</tr>
<tr>
<td>Target INR 2.5 n (%)</td>
<td>3,076 (65.6)</td>
<td>2,581 (70.8)</td>
<td>495 (48.1)</td>
</tr>
<tr>
<td>Target INR 3.0 n (%)</td>
<td>400 (8.5)</td>
<td>158 (4.3)</td>
<td>242 (23.5)</td>
</tr>
<tr>
<td>Diabetes %</td>
<td>10.9</td>
<td>10.4</td>
<td>12.4</td>
</tr>
<tr>
<td>Hypertension %</td>
<td>28.9</td>
<td>29.4</td>
<td>27.1</td>
</tr>
<tr>
<td>Previous stroke/TIA %</td>
<td>11.9</td>
<td>11.3</td>
<td>13.9</td>
</tr>
<tr>
<td>Liver disease %</td>
<td>0.6</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Kidney disease %</td>
<td>3.2</td>
<td>2.8</td>
<td>4.6</td>
</tr>
<tr>
<td>COPD %</td>
<td>3.6</td>
<td>3.1</td>
<td>5.2</td>
</tr>
<tr>
<td>Atrial fibrillation %</td>
<td>34.5</td>
<td>28.1</td>
<td>56.6</td>
</tr>
<tr>
<td>Heart failure %</td>
<td>27.0</td>
<td>21.9</td>
<td>44.5</td>
</tr>
</tbody>
</table>

*Includes patients with both aortic and mitral prostheses
Total rate of thromboembolic events was 2.30 (of which 1.33 were arterial) per 100 treatment years. There was no significant difference between prostheses in different positions. Rate of major bleeding per 100 treatment years among all patients was 3.16 (of which 0.49 were intracranial). Total mortality rate among all patients was 2.42. Both the rate of bleeding complications (excluding GI bleedings) and death were significantly higher in patients with a MHV prosthesis in the mitral position compared to the aortic position (Table 10).

Table 10. Rate of complications per 100 treatment years with 95% confidence interval.

<table>
<thead>
<tr>
<th></th>
<th>All patients n=4,687</th>
<th>Aortic valve n=3,656</th>
<th>Mitral valve n=1,031*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleedings</td>
<td>3.16 (2.91-3.43)</td>
<td>2.87 (2.61-3.16)</td>
<td>4.37 (3.71-5.11)</td>
</tr>
<tr>
<td>CNS</td>
<td>0.49 (0.39-0.60)</td>
<td>0.41 (0.31-0.52)</td>
<td>0.84 (0.57-1.19)</td>
</tr>
<tr>
<td>Thromboses</td>
<td>2.30 (2.09-2.53)</td>
<td>2.26 (2.03-2.52)</td>
<td>2.46 (1.98-3.03)</td>
</tr>
<tr>
<td>Death</td>
<td>2.42 (2.2-2.65)</td>
<td>2.16 (1.93-2.41)</td>
<td>3.50 (2.92-4.17)</td>
</tr>
</tbody>
</table>

*Includes patients with both aortic and mitral prostheses

Mean TTR was 72.5%. Patients with prosthesis in the aortic position had a higher TTR than those with a mitral prosthesis. Mean INR was 2.65.

All complications had a significantly higher rate (p<0.001) in patients with lower TTR (≤70%) compared with TTR >70% (Table 11). Comparison after dividing into quartiles reveals a higher complication rate in total as well as bleedings, thromboses and death separately in quartiles I to III (with the exception of thromboses in quartile III) compared with the best quartile.

Lower INR variability (<0.40) compared with higher INR variability (≥0.40) was associated with a significantly (all p <0.001) lower rate of all and any type of complications (Table 11). When divided into quartiles, a significantly higher rate of all and any complications was apparent in the two quartiles with the highest INR variability compared with the best quartile. The exception was mortality which occurred significantly more often only in quartile I with the highest INR variability.
Table 11. Rate of complications per 100 treatment years with 95% confidence interval, according to warfarin treatment quality measured as TTR or INR variability, using TTR 70% or the mean INR variability of 0.40 as cut-off.

<table>
<thead>
<tr>
<th>Variability</th>
<th>TTR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤0.4000</td>
</tr>
<tr>
<td>Bleedings</td>
<td>2.00 (1.71-2.31)</td>
</tr>
<tr>
<td>Thromboses</td>
<td>1.82 (1.55-2.13)</td>
</tr>
<tr>
<td>Death</td>
<td>1.51 (1.26-1.79)</td>
</tr>
</tbody>
</table>

Taking both TTR and INR variability into consideration we divided patients into four groups. The group with the best treatment quality had high TTR and low INR variability (divided according to the same principle as above) and was compared with the other groups (high TTR and high INR variability, low TTR and low INR variability), and the group with the lowest treatment quality (with low TTR and high INR variability). The group with the best treatment quality had the lowest risk of complications. Patients with high variability and high TTR had a higher risk for all complications compared to low variability. Patients with low TTR and low variability had a higher risk for bleedings and death than the first group with high TTR and low variability, though not when compared with those with high TTR and high variability. Finally, the group with low TTR and high variability had a higher risk of bleeding and death when compared with those with high TTR regardless of INR variability. They also had a higher risk of thromboses when compared with the best group, but did not differ in the risk for any complication compared with those with the same TTR but lower INR variability. Comparison of target INR 2.5 versus 3.0 among all patients independently of valve prosthesis location reveals that a higher target INR had a significantly higher risk of all complications, bleeding and thrombosis compared with a lower target INR (Table 12). Target INR does not necessarily reflect the patients’ actual INR. Therefore, we divided the patients into two groups by actual mean INR. One group consisted of patients with lower values between 2.2 and 2.7 (corresponds to a target INR 2.5) while the second group consisted of patients with higher values between 2.8 and 3.3 (corresponds to a target INR 3.0). Comparison of these two groups indicates that higher INR levels are associated with a significantly higher risk for complications in total, and for bleedings and death (Table 12).
Table 12. Risk of complications (HR) depending on warfarin treatment intensity as measured by actual mean INR and target INR.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Thromboses</th>
<th>Bleedings</th>
<th>Death</th>
<th>All compl.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual INR</td>
<td>2.2-2.7</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>INR</td>
<td>2.8-3.3</td>
<td>0.97, p=NS</td>
<td>1.29, p=0.02</td>
<td>1.65, p&lt;0.001</td>
</tr>
<tr>
<td>Target INR</td>
<td>2.5</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>INR</td>
<td>3.0</td>
<td>1.74, p=0.003</td>
<td>1.58, p=0.009</td>
<td>1.44, p=NS</td>
</tr>
</tbody>
</table>

HR is adjusted for MHV prosthesis position, AF, Heart failure, Hypertension, Diabetes, Stroke and Age.
DISCUSSION

Study population
Study I included all patients treated with warfarin who were registered in Auricula during the study period. Data from Auricula were merged with the National Patient Registry, which has a positive predictive value of 85 to 99% (depending on diagnosis). There were no exclusion criteria.

Study II covered a slightly smaller population of patients limited to patients with target INR of 2.5. To our knowledge these are the largest studies conducted on this type of patients.

Study III included all patients from Sundsvall and Malmö with a mechanical heart valve prosthesis who were registered in Auricula during the study period. Only two patients were excluded at the beginning; one, who after reading the information letter declined to participate, and one with a tricuspid valve prosthesis, because it is not possible to perform a statistical analysis on one patient. Nine patients were subsequently excluded due to lacking INR data, which made calculation of TTR impossible. This gave a loss of only 1.7 % from the primary study group.

Comparison of these patients with the population in Study IV, which is larger but only includes data from registries revealed few differences. There were no significant differences in age, sex or TTR, which indicates that these are the same type of patients. One distinct difference is comorbidity, in particular the percentage of patients with hypertension (twice as many in Study III). At the same time, no great difference in previous stroke/TIA could be observed. This indicates that comorbidity is underreported in registries, certainly for “less serious” and common diseases such as hypertension. This is probably because secondary diagnoses are not listed in hospital discharge cards. In Study III, data were collected manually from medical records, drug prescriptions and primary care medical records allowing detection of all patients with hypertension, for example, regardless of whether the ICD-10 diagnosis has been listed in the medical records.

Comparison of patients with aortic valve prostheses with those with mitral valve prostheses revealed that there was a higher percentage of women with a prosthesis in the mitral position (over 50%; in contrast only about 30% of patients with an aortic prosthesis were women) and those patients had more co-morbidities (in addition to hypertension). Their treatment was also less well-controlled when measured using TTR. This can probably be explained in part by the fact that many patients with mitral valve prostheses have a higher target INR range (2.5-3.5)
while TTR has been calculated for the interval 2.0-3.0. In other words, patients having an INR of 3.1, for example, would lie outside the TTR range while at the same time receiving correct treatment.

Study IV included all patients with a mechanical heart valve prosthesis in Sweden registered in AuriculA. Again, only patients with a tricuspid prosthesis (n=10) and 134 patients who lacked information on TTR were excluded. This gives a loss of approximately 4%.

Also here, the differences between patients with a valve prosthesis in different positions are noticeable, and are in line with Study III, although the differences are slightly smaller. To our knowledge, this is the largest study on patients with mechanical heart valve prostheses. The second largest was conducted by Butchart et al. [109] who analysed 10,203 treatment years. However, it was performed before standardization of PK (%). Moreover, it only considered the number of INR samples outside the therapeutic range, ignoring time between samples, which is included in TTR.

Other studies on this topic have mainly been conducted in the 1980s and 1990s [110,111]. As mentioned above, PK (%) at that time was not standardized and a same sample could give completely different results when analysed by different laboratories. Since then, mechanical heart valve prostheses have developed dynamically making these studies obsolete and no longer relevant.

In summary, there is a lack of well-conducted, recent studies on patients with mechanical heart valve prostheses, which has resulted in uncertain and varying recommendations regarding anticoagulant treatment. With our studies, we are endeavouring to fill this gap using modern data from real-life, and applying them to every-day patient care.

All of the studies presented in this thesis were conducted on wide, unselected populations and as few exclusion criteria as possible. Even though the studies were not randomized, we do believe that, because we have not excluded any patient group, our study population(s) reflects the real-life population in Sweden. This means the study results are reliable and enables them to be transposed into everyday clinical practice.

By using ICD-10 classification we could unify all the complications. This meant that every complication as well as every concomitant disease corresponds and has the same ICD-10 code(s). On the one hand, this is of course positive as the clear definitions make the data replicable and comparable with other studies/populations. On the other hand, the quality of the data is dependent on doctors setting a diagnosis and assigning an ICD-10 code. In some cases, medical secretaries code a diagnose in ICD-10. This is the weakest point of these codes
as it is completely person-dependent and cannot be controlled by a researcher. This can result in bias in the form of both under- and over-reporting.

**Quality of warfarin treatment in Sweden**

Sweden is one of the world-leaders in regard to quality of treatment with warfarin. This is, at least in part, the result of highly organized patient care provided by specialist nurses in outpatient clinics. The quality of treatment can be measured directly by the number of complications, major bleedings, thromboses and death, or indirectly by the following methods:

- the time the patient lies within the therapeutic range (TTR – time in therapeutic range, in our studies calculated according to the Rosendaal method) [87]
- INR variability (calculated according to the method described by Fihns et al.) [89,90,92]
- the proportion of INR samples within the therapeutic range (hit rate)
- the mean or median deviation from the target INR.

Of the indirect methods, the most popular in the literature is TTR. A number of studies have consistently reported a very high TTR (around 75%) in Swedish patients treated with warfarin. [112-114] Our study has confirmed this finding, with a mean TTR of 76.5%. This result was obtained using a large, unselected, real-life population. In comparison, in pivotal studies for NOACs (RE-LY, ROCKET and ARISTOTLE trials) the average TTR levels lie between 55 and 64% [115-117], which is significantly lower. Moreover, no patients were excluded in our study, which means that there were more senile patients and patients with multiple concurrent conditions than in randomized clinical trials using inclusion and exclusion criteria. In other words, if our study population had been selected using the same criteria it is possible that the TTR would have been even higher.

Looking at the direct measurement of treatment i.e. bleeding and thromboembolic complications, these too have given better results than the studies mentioned above. In the NOAC studies, the patient control group treated with warfarin had an annual risk of bleeding between 3.09 and 3.57% depending on the study. In our study, the corresponding figure was 2.18%. This may depend in part on a potential underestimation of bleeding complications due to the study design – register studies are prone to underreporting compared to prospective
clinical trials. On the other hand, this difference could be the effect of a significantly higher TTR in our study population.

Of all the complications of warfarin treatment, the most feared is intracranial bleeding. In our population the annual risk was 0.37% in the whole group, and 0.38% in patients with atrial fibrillation. This is comparable with the annual risk of bleeding in patients treated with NOACs. In the NOAC studies mentioned above [115-117], the annual risk of bleeding in patients receiving warfarin was between 0.7 and 0.8%. In our study, such bleeding rates occurred only in patients above 90 years of age.

Having a mechanical heart valve prosthesis is related to a higher risk of bleeding. This may be the effect of a higher target INR (2.5-3.5 compared with the most common 2.0-3.0) in a significant group of patients.

To our knowledge, this is the largest study conducted on patients receiving high quality treatment with warfarin. The study included more than 77,000 patients with more than 100,000 prescribing periods and almost 218,000 treatment years. This should minimize potential bias resulting from the study design.

**Effect of computer aided dosing on treatment quality**

As stated above, the quality of warfarin treatment in Sweden is outstandingly high. But, could it be even higher with the assistance of software?

Previous studies [118-122] have shown that it is possible to improve the quality of treatment using computer aided dosing. These studies however were small and conducted on populations with a low quality of treatment measured using TTR (between 48 and 68% in control groups). This made it relatively easy to improve quality. These studies took cTTR into consideration. One study conducted in a high TTR environment with TTR about 80% compared two different algorithms. Our study is the first and, to our knowledge, the largest (with almost 54,000 patients from 125 centres and over 1 million INR samples) to compare computer dose suggestions with those manually changed at the individual level. Moreover, due to the very good treatment quality in Sweden our study was conducted in a high TTR setting with a TTR exceeding 75%, which (as mentioned above) has repeatedly been reported in the Swedish patient population.

AuriculA’s dosing algorithm aims to improve the treatment quality and to standardize treatment for all patients regardless of whether they are treated in a small primary care clinic or a University hospital in a big city. It also has the capacity to improve over time because of
the retrospective analysis of each dosing rule outcome, and comparison with manually changed doses. This study shows that in most cases algorithmic suggestions perform better than those manually changed. On the one hand, it is possible that the changes are made because of knowledge that could influence the warfarin treatment. At the same time the suggestion itself (because it is always presented for acceptance/rejection) can affect the manually changed dose.

One could assume that the algorithm would improve the quality of treatment mostly at centres with less experience, but our study reveals a weak trend indicating that acceptance of algorithm suggestions is higher at centres with higher cTTR. Another observation is that even though the algorithm is designed to be cautious and is intended to keep the INR close to the target INR of 2.5, accepted suggestions still result in higher INR values compared with those manually changed. This confirms the supposition that doctors prescribing warfarin tend to keep INR to the lower limit of the target INR range, often resulting in under-dosing [121].

Not surprisingly, it is better to have detailed knowledge of treatment history. Suggestions based on three or more previous INR values were more accurate than those based only on two values. This applies to both manual and algorithmic prescriptions. The algorithm follows 720 rules. Some of them do not perform as well as their manual analogues. These have now been adjusted or changed to suggest that dosing is to be done manually. Their outcome will be analysed in future algorithm evaluations.

This was a retrospective study without randomization, which makes it impossible to rule out bias. The prescribing physician may have been aware of information on concurrent diseases, co-medication or forgotten warfarin doses that was not available to the algorithm. And the algorithm suggestion could have influenced the person responsible for the prescription. The included centres are not homogeneous regarding the number and type of patients, indication for treatment, experience and TTR. On the other hand, no centres or patient groups are excluded which means that the study population reflects everyday clinical practice and includes all types of patients treated with warfarin.

In summary, the results of our study show that computer aided dosing can improve the quality of treatment even for patients with a pre-existing high treatment quality and thereby enable reduction of the risk of serious complications.
Quality of treatment in patients with mechanical heart valves
As mentioned above, the quality of treatment was high and the risk of complications low in a wide, unselected population of patients treated with warfarin. But what happens in a more specific population with mechanical heart valve prostheses?

In Study I, we have looked more closely at this patient group and found that they have a higher risk of bleeding. This applied to the overall risk of bleeding as well as the individual risks of intracranial bleeding, gastrointestinal bleeding and other bleeding. This can probably be explained by the fact that in this group there is a relatively (compared to other treatment indications) large proportion of patients with a higher target INR (3.0 (corresponding to range 2.5-3.5) compared with the most common INR of 2.5(2.0-3.0)). Surprisingly, these patients did not have a concomitant lower risk of thromboembolism. Female gender was associated with a higher risk of bleeding in general, though paradoxically with a lower risk of intracranial bleeding even though the women had a higher age and lower mean TTR.

Studies III and IV looked specifically at this patient group.

Study III was conducted on a smaller population of patients from Malmö and Sundsvall who had mechanical heart valve prostheses. The study cohort consisted of 534 patients. This may not appear to be a large study but data on complications and comorbidity were collected very carefully by only two investigators, and hopefully very little data were missed.

Study IV on the other hand was conducted on all patients with mechanical heart valve prosthesis in Sweden treated with warfarin and registered in AuriculA during the study period. This makes it, to our knowledge, the largest study in this area since the standardization of PK.

In Study III, we investigated whether the risk of complications is affected by TTR and in Study IV we also looked at INR variability, both alone and in combination with TTR, and its influence on the risk of complications. We have also raised the issue of the target INR for this group of patients.

TTR
The relationship between TTR and the risk of complications has been previously studied in patients with atrial fibrillation [88] and TTR has been shown to affect the risk of complications. However, no studies have been conducted investigating such a relationship in patients with mechanical heart valve prostheses. One exception is a retrospective study conducted in a high TTR setting, but with a broad therapeutic INR range and on patients with several indications for treatment [123].
In Study I, a mean TTR of 74.5% was found, which was lower than the mean TTR in the whole study population and for any other group of patients. But this is very high compared with other countries or NOAC pivotal studies.

In Study III, the mean TTR for our patients was 71.3%. This is slightly lower than in Study I. This may depend in part on the fact that the study population in Malmö was older and therefore had probably more concomitant diseases, which could have influenced the TTR value. Mean TTR was lower in women (68.2%) than men (73.1%), and probably depends on the fact that women were overrepresented among patients with mitral heart valve prostheses, whereas they comprised only about 32% of patients with a prosthesis in the aortic position. This difference is hard to explain as we lack data on the indication(s) for valve implantation.

In Study IV, the mean TTR was 72.5% (in line with the studies above) and was distinctly higher in patients with a prosthesis in the aortic position.

In the smaller study we observed a correlation between TTR and the risk of complications at the individual level. There was a higher risk of bleeding and death with decreasing TTR (divided into quartiles). At the same time, no relationship was found between TTR and the risk of thromboembolism. It is likely that a TTR of 70% or more is adequate to prevent valve thrombosis (with the reservation that our study is too small to provide evidence for this hypothesis). Another factor that could affect our results is the common practice of using low molecular weight heparin (LMWH) prophylaxis for sub-therapeutic PK (INR), which occurs more often in patients with a lower TTR.

Study IV, which was conducted on a significantly larger population of 3,831 patients with mechanical heart valve prostheses with over 18,000 treatment years on warfarin, confirmed most of our findings.

cTTR under 70% (suggested TTR for patients with AF from previous studies [124,125]) was associated with a doubled rate of bleedings and mortality. We also noticed a 50% increase in the rate of thromboembolic complications (which was not present in the smaller study).

Together, this confirms our hypothesis from Study III that a TTR of 70% or more is sufficient for adequate treatment with a low rate of complications.

**INR variability**

INR variability is another indirect method of measuring quality of treatment with warfarin. A study by Vanerio et al. [126] has shown that it can be used successfully to assess the quality of anticoagulation treatment in patients with AF. Another study by Labaf et al. compared INR
variability and TTR prediction ability to assess the risk of complications such as thromboembolism, major bleeding and death in patients with MHV. The results were comparable. Study IV confirms those findings. Higher INR variability was associated with an increased rate of all types of complications including thromboembolism when compared with those with more rigorous INR control.

However, when we compare INR variability and TTR (both divided in quartiles) we can see that the association between treatment quality with warfarin and the risk of complications was higher for TTR.

**TTR and INR variability combined**

No previous study has aimed to investigate the impact of both TTR and INR variability combined on the risk of complications in patients with mechanical heart valve prosthesis. We have attempted to study if such an association exists. We divided patients into four groups and paired them in a way that patients with high TTR ≥70% were divided into two groups (low or high risk) depending on their INR variability. Patients with a lower TTR <70% were divided similarly. Indisputably the group with both high TTR and low INR variability had the lowest risk of complications. Patients with the same high TTR level but with a higher INR variability had a higher risk of all complications (bleedings, thromboembolism and death) confirming the role of INR variability in risk assessment. At the same time, low INR variability is not enough. When we compared patients with low versus high TTR in the same low variability setting, we saw that those with a lower TTR had a higher mortality and risk of bleeding (but not of thromboembolism).

TTR is calculated for a relatively broad INR range between 2 and 3, which means that patients with a high TTR could still have a high INR variability. On the other hand, those with higher (2.5-3.5) INR target with a higher mean actual INR as a consequence (e.g. 3.1) could have a low TTR despite a low INR variability, resulting in an increased risk of bleeding. This means that to reduce the risk of complications it is important to concentrate not only on maintaining a high TTR but also to keep INR values stable.

It also gives rise to another important question – what is an optimal target INR for patients with mechanical heart valve prostheses?

**Target INR**

As mentioned earlier, current recommendations for target INR for patients with mechanical
heart valve prostheses vary, lacking support from large, randomized studies and being based mainly on expert opinion. In addition, the target INR is currently defined differently for each prosthetic valve position. Most of the patients with an MHV in an aortic position have a target INR of 2.5 (range 2.0 – 3.0) whereas those with an MHV in a mitral position more frequently have a target INR of 3.0 (2.5 – 3.5). However, this is a theoretical difference. In clinical practice, patients with an intended INR can have an actual mean INR in the higher or lower end of the target INR range. We have therefore divided patients with mechanical heart valve prostheses into two groups based on their actual mean INR, 2.2-2.7 or 2.8-3.3, corresponding to the lower or higher end of the treatment range irrespective of the intended INR target level.

We compared patients from one of the above groups; it was not possible to observe any supremacy of the higher actual INR values in regard to complications, regardless of whether the prosthesis was in an aortic or mitral location. One possibility is that we do not have all the information on comorbidity and other factors that could contribute to selection bias to a higher or lower actual INR.

We found only one significant difference; patients with MHV in an aortic position in the higher mean INR group had a higher risk of death. This is difficult to explain. Even after multivariable adjustment for comorbidity, age and sex no difference in favour of higher treatment intensity could be observed.

Furthermore, a higher actual mean INR was associated with a higher risk of all complications and death regardless of the position of the prosthesis. In other words, a higher intensity of treatment not only did not have any benefit, but could even be harmful to patients.

There is a need for larger, randomized, prospective studies to identify optimal INR levels; unfortunately it is unlikely that such studies will be conducted.

Nevertheless, our study indicates that an INR between 2.0 and 3.0 could be sufficient even for patients with a mitral mechanical prosthesis.

If a target INR range between 2.0 and 3.0 was used for the majority of patients, regardless of valve type or location, we could probably avoid a number of bleeding complications without increasing the risk of thromboembolic complications or death.

Moreover, a unified target range would make it easier to standardize treatment in this challenging group of patients, and to keep TTR at a high level and INR variability low.

**Register studies**

All our studies are registry studies. Apart from Study III, which is only based in part on registries (remaining data were collected directly from patient medical records), all other
studies were observational, non-randomized retrospective studies conducted only on data from registries. This study design has both advantages and disadvantages. The biggest advantage is probably the mere size of the study cohort. Our study population included over 70,000 patients with over 200,000 prescription periods, which, to our knowledge, makes these studies the largest conducted in this area. Prospective, randomized clinical trials of this size would of course be of great value but due to inter alia economic reasons will never be conducted. Another major advantage mentioned previously is that our study population consists of unselected patients from both specialist clinics and primary healthcare. This means that our cohorts (and studies) reflect real-life and are generalizable. The cohort size has also enabled us to register a large number of events. Finally, these studies are relatively inexpensive which has enabled them to be conducted without external sponsors (e.g. pharmaceutical companies) and any consequent potential conflict of interests. On the other hand, they have some serious disadvantages. Firstly, the data quality is variable and questionable as it is registered by different people in different situations. The data have been registered without alignment with the specific study question; in randomized trials investigators focus on specified data. This can result in an underestimation of comorbidity and underreporting of endpoint events. For example, we may have missed minor bleedings that would have been noted in a randomized trial, but which, as they would have been treated in primary care would not have been recorded in our study. Because we have only considered primary diagnoses, endpoints registered as secondary diagnoses would have been missed. This underreporting is clearly seen when we compare patient populations from Studies III and IV. The underestimation regarding comorbidity is high. At the same time, more serious and life-threatening diagnoses such as stroke or TIA are well-reported even in registries. It is therefore impossible for example to calculate patients’ CHADS score based only on registry data.

In summary, register studies have their disadvantages, primarily the risk of underreporting endpoint events because these are more sensitive to human error than in randomized clinical trials. On the other hand, it is unlikely, that we have missed the most serious and dangerous complications such as intracranial bleedings. The character of the study cohort (large, unselected) makes our results transposable to everyday clinical practice.
**Limitations**

An individual researcher cannot verify the quality of data obtained from registries. The quality of the data depends on the accuracy of the person entering the data in the register. This is a limitation in Studies I, II and IV. Study III is to some extent dependent on registry data, but the data were also confirmed by thorough review of patient medical records undertaken by the researchers themselves.

AuriculA covers approximately 50% of patients undergoing anticoagulant treatment with warfarin in Sweden. This means that data on the remaining 50% are lacking in our studies. On the other hand, no patient groups are excluded from the registry and when introduced it covered entire counties and both specialist clinics and primary care.

The positive predictive value for diagnoses in the Patient Register lies between 85 and 99% depending on the diagnosis [127]. There is little knowledge on the negative predictive value for most diagnoses due to the fact that this requires knowledge on the genuine prevalence of diseases in the population, including those who have not yet received a diagnosis. Consequently, registry studies tend to underestimate, rather than overestimate, comorbidity.

In Studies I, II and IV we were not able to verify the sensitivity of the detection of endpoint events. For example, it is likely that minor bleedings (which would have been registered in a prospective study) were treated in primary care and consequently were not reported. Some of the endpoints could also have been registered as secondary diagnoses and were therefore not taken into account. Furthermore, patients who were not hospitalised when they died would not be registered; this could also lead to underestimation of endpoint events.

Some of the patients failed to achieve stable anticoagulation with warfarin (expressed as stabile INR values) and were therefore taken off the treatment. The extent of these unplanned terminations of treatment is unknown, and could constitute a selection bias in Studies I, II and IV.

In Study II, in which we evaluate the dosing algorithm, it is possible that information was available (e.g. forgotten warfarin dose or change in co-medication) to the person responsible
for the finale dosage, and which could have influenced their decision. Moreover, as algorithmic suggestions are not blinded these could also have affected a final decision. Centres included in this study differed from each other in regard to the number of patients, treatment indications, warfarin dosing experience, and treatment quality as measured by TTR. Nonetheless, no centres or patient groups were excluded.

In Studies I, II and IV one of the complications was major bleeding which we have defined in accordance with the International Society of Thrombosis and Haemostasis, i.e. fatal bleeding, and/or equivalent blood loss greater than 20 g haemoglobin/L, requiring transfusion of at least 2 units of blood, and/or bleeding verified by diagnostic radiology, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome [128]. As there were no data available in the Patient Register on the number of blood transfusions or decrease in haemoglobin it is possible that we have underestimated bleeding frequency according to the ISTH definition. On the other hand, a haemoglobin reduction or blood transfusion that does not result in a separate bleeding ICD-10 diagnosis, is probably less serious than the complications we have included. In Study III, we manually checked the patient records, including laboratory tests and prescriptions, which provided data missing from the Patient Register.
Implications
Despite the introduction of NOACs, warfarin is still a valid treatment option for patients requiring oral anticoagulation and the only option for patients with a mechanical heart valve prosthesis.

This thesis has shown that even though Sweden is a world-leader in treatment with warfarin, there is still room for further improvement. Introduction of a computer-aided dosing system (in this case, AuriculA) would probably allow standardization of warfarin treatment and increase the treatment quality for the remaining patient population who are not currently included in the registry. Furthermore, the work covered by this thesis demonstrates that to assess quality we should look not only at Time in Therapeutic Range but also INR variability and endeavour to maintain this at as low a level as possible.

Moreover, we indicate that it is possible that unifying the target INR at 2.5 (range 2.0-3.0) for all patients with a mechanical heart valve protheses would enable a reduction in the number of adverse events. Our data did not realise any advantage of higher treatment intensity. Because our findings come from retrospective studies, there is a need for prospective randomized trials to confirm them.
Conclusions

- Quality of treatment with warfarin in Sweden regardless of indication is very high.
- Well-controlled warfarin treatment with TTR exceeding 75% is both safe and effective.
- The existing high quality of treatment can be further improved using computer-aided dosing.
- In order to reduce the risk of serious complications it is important to achieve and maintain a high quality of treatment with warfarin that takes into account both high TTR and low INR variability.
- The aim should be a TTR of 70% or higher and an INR variability lower than 0.40.
- A target INR of 2.5 (range 2.0 – 3.0) is associated with the lowest risk of complications regardless of valve type or location, and a higher treatment intensity has not been observed to offer any benefits.
Future considerations

The findings covered by this thesis could result in changes in anticoagulation treatment care in Sweden, in particular for patients with mechanical heart valve prostheses.

Firstly, it should be endeavoured to introduce a computer-aided dosing system in all healthcare units that manage anticoagulant treatment as this can, and does, raise the quality of treatment, even though this is currently higher in Sweden than in other countries.

Furthermore, the same system/program should be implemented throughout the country to harmonise and standardize treatment quality.

Moreover, it is worth considering the use of TTR and INR variability treatment checks to identify patients at higher risk of complications; this would enable more focus on those patients and prevention of a number of complications.

Last, but not least, the target INR ranges in patients with a mechanical heart valve prosthesis should be reconsidered. Of course, this is a registry study, which makes it harder to draw conclusions and larger, randomized studies are needed to confirm or reject our hypothesis. Unfortunately, the financial considerations make it quite unlikely that such studies will be conducted.

Warfarin will remain the only treatment option in the foreseeable future for patients with mechanical heart valve prostheses and efforts should be continuously made to improve this therapy.
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