Management of Adults with Congenital Heart Disease

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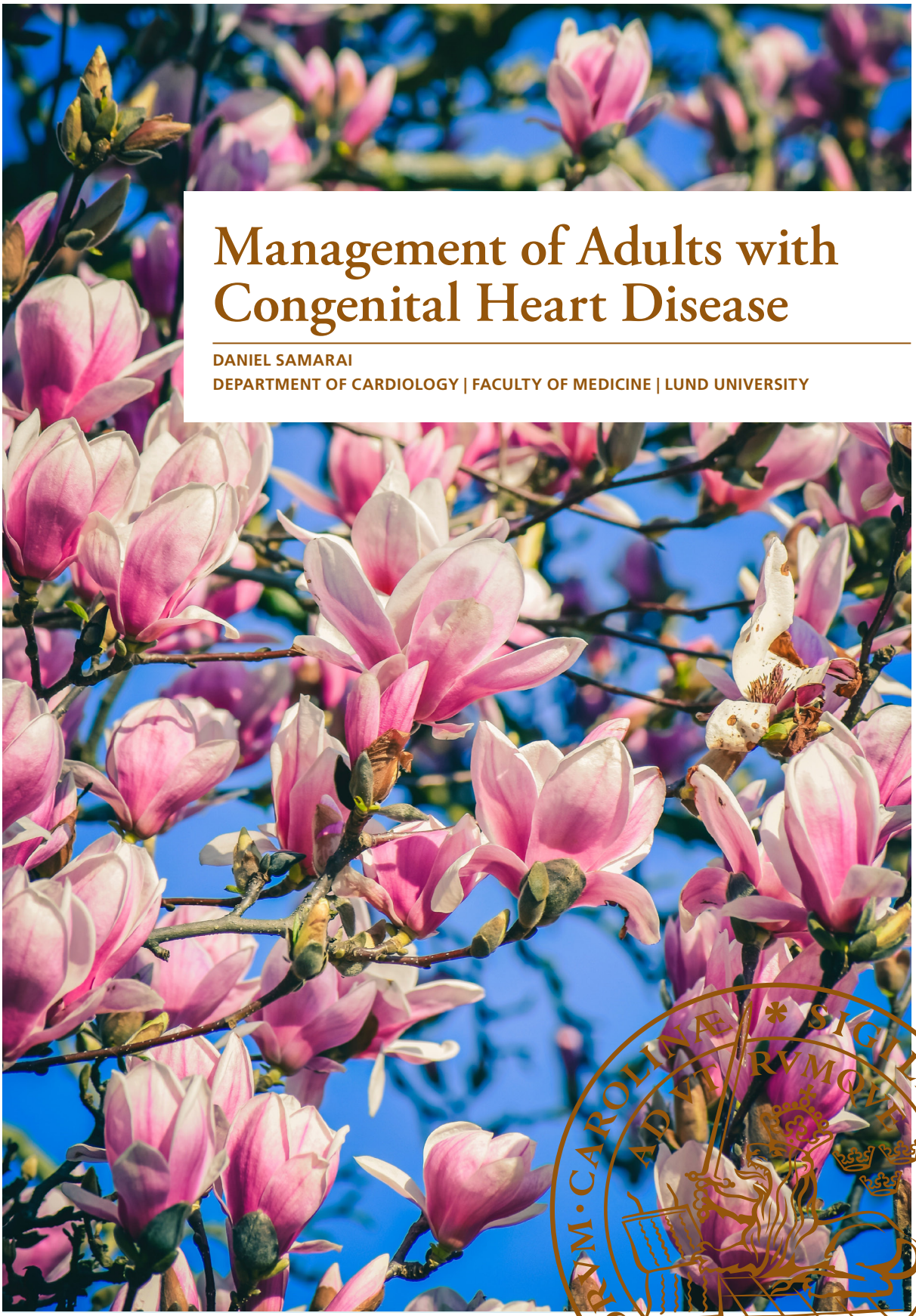

Management of Adults with Congenital Heart Disease

DANIEL SAMARAI
DEPARTMENT OF CARDIOLOGY | FACULTY OF MEDICINE | LUND UNIVERSITY

Management of Adults with Congenital Heart Disease

Daniel Samarai

LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Abstract

Adults with congenital heart disease (ACHD) are a completely new and rapidly growing specialty comprising patients who require specialist knowledge regarding their care and treatment. Challenges involve diagnostics and treatment as studies are scarce and include small and heterogenous study populations.

The first aim with this thesis was to evaluate the relationship between the systemic right ventricular function determined by cardiac magnetic resonance (CMR) imaging, biomarkers, echocardiographic parameters, New York Heart Association class and performance on stress test.

The second aim of this thesis was to evaluate anticoagulation treatment with vitamin K antagonists (VKA) in ACHD. This involved determining the quality of VKA therapy by evaluating time in therapeutic range (TTR) and variability of international normalised ratio of prothrombin time. Furthermore, studying the efficacy and safety of VKA and non-vitamin K oral antagonists (NOAC) in ACHD by evaluating the incidence of thromboembolism (TE), major bleeding and potential risk factors.

Paper I A correlation was observed between the systemic ventricular function determined with CMR and echocardiographic ventricular global longitudinal strain in patients with systemic right ventricle.

Paper II-III Anticoagulation with VKA was of high quality in ACHD in the South of Sweden. A low incidence of TE and major bleeding events was seen in ACHD patients with high quality VKA treatment. Younger age, female gender and cardiac failure were risk factors for poor anticoagulation and thus may be cause for cautiosness and when suitable, consideration of alternative non-VKA anticoagulants. History of TE was associated with complcations (TE and major bleeding).

Paper IV In this retrospective study reports a single-center experience of NOAC use in ACHD patients we found no thromboembolic and one major bleeding events during a median duration of 17 months of therapy.

In conclusion, right ventricular global longitudinal strain by echocardiography may be useful in the evaluation of the systemic right ventricular function in patients with congenitally corrected transposition of the great arteries (TGA) or TGA after atrial switch.

Anticoagulation therapy with oral VKA is of good quality in ACHD patients with a high TTR, low INR variability, low incidence of TE and major bleeding events. We recommend the applicable target of TTR>65% for ACHD patients. Young age and female gender may be considerable factors to consider when initiating anticoagulation therapy. NOAC therapy may be considerable in the absence of highly specialized organization in regard to VKA medication where close monitoring of the patient is not possible. NOAC appear safe and effective in ACHD patients without mechanical valve protheses.

Larger prospective trials on efficacy and safety of VKA and NOAC in ACHD would be needed to develop and further improve the treatment guidelines.

Key words: adult congenital heart disease, anticoagulation, thromboembolism, vitamin K antagonists

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Daniel Samarai

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This thesis is dedicated to Mom and Dad

"A joyful heart is good medicine.
But a broken spirit dries up the bones"
Proverbs 17:22

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List of abbreviations

ACHD	adults with congenital heart disease
AF	atrial fibrillation
AHA	American Heart Association
AP4	apical 4 chamber
ASD	atrial septal defect
AuriculA	National Quality Registry for Atrial Fibrillation
AV	atrioventricular
BNP	B-type natriuretic peptide
CHD	congenital heart disease
CI	confidence interval
CMR	cardiac magnetic resonance imaging
FAC	fractional area change
GLS	global longitudinal strain
INR	international normalised ratio
IQR	interquartile range
LVEF	left ventricular ejection fraction
NOAC	non-vitamin K oral anticoagulants
NT-proBNP	N-terminal proB-type natriuretic peptide
NYHA	New York Heart Association
OR	odds ratio
RVEF	right ventricular ejection fraction
SAX	basal short axis
SD	standard deviation
SWEDCON	SWEDish registry on CONgenital heart disease
TAPSE	tricuspid annular plane systolic excursion
TE	thromboembolism
TEE	transoesophageal echocardiography
TGA	transposition of the great arteries
TIA	transient ischaemic attack
TTE	transthoracic echocardiography
TTR	time in therapeutic range
VE/VCO_2	ventilation to carbon dioxide output
VKA	vitamin K antagonist
VTE	venous thromboembolism

List of original papers

This thesis is based upon the following papers, referred to as Papers I-IV.

I. Global longitudinal strain correlates to systemic right ventricular function. **Samarai D**, Lindstedt S, Gustafsson R, Thilen U, Hlebowicz J. Cardiovasc Ultrasound. 2020 Jan 27;18(1):4.

II. Quality and predictors of oral anticoagulation therapy with vitamin K antagonists in adult congenital heart disease: TTR and INR variability. **Samarai D**, Isma N, Lindstedt S, Hlebowicz J. Thromb Res. 2021 Sep 1;207:7-9.

III. Incidence and risk factors for thromboembolism and major bleeding in adults with congenital heart disease taking vitamin K antagonist therapy. **Samarai D**, Lindstedt S, Isma N, Hlebowicz J. (Unpublished manuscript, submitted).

IV. Novel oral anticoagulant use in adults with congenital heart disease: A single-center experience. **Samarai D**, Isma N, Lindstedt S, Hlebowicz J. (Unpublished manuscript, submitted).

Aim

The overall purpose of the studies was to improve the management, including diagnostics and treatment, in adults with congenital heart disease (ACHD).

Paper I

The aim of this retrospective study was to evaluate the relationship between right ventricular function derived from cardiac magnetic resonance imaging (CMR), echocardiography and exercise stress test performance, NT-proBNP (N-terminal proB-type natriuretic peptide) level and New York Heart Association (NYHA) class in patients with a systemic right ventricle.

Paper II

The aim of this study was to investigate time in therapeutic range (TTR) and international normalised ratio (INR) variability in ACHD patients and to evaluate previously reported predictors.

Paper III

The aim was to determine the incidence of thromboembolic- and major bleeding events in ACHD patients on vitamin K antagonist (VKA) therapy.

Paper IV

The aim was to report our experience of novel oral anticoagulants (NOAC) in ACHD patients, including the incidence of thromboembolism (TE) and major bleeding events.

Adults with congenital heart disease

In the 1950s, approximately 15% of children with congenital heart disease (CHD), the most common inborn and global defect, survived to adulthood. Today, the number is closer to 90% (1), resulting in an expanding patient group, ACHD. In 2008 for the first time, ACHD patients in the European Union exceeded those of children with CHD (2). The reasons for the improved prognosis are improvements in paediatric cardiology, cardiac surgery and catheter interventions. Arterial and atrial switch procedure for transposition of the great arteries (TGA) is one example, another is the Fontan operation for "single ventricle" and percutaneous interventions such as pulmonary valve implantation (1). 1944 was a special year, marked by two great milestones. It was the year in which Clarence Crafoord at Karolinska Hospital in Sweden performed the first successful repair of aortic coarctation (3). The same year at Johns Hopkins University in Baltimore, USA, surgeon Alfred Blalock, together with paediatric cardiologist Helen B. Taussig, developed the shunt to palliate patients with cyanotic CHD, turning blue babies to pink within minutes (4).

Although improved care of CHD has enabled survival into adulthood, most defects are not cured, which is why specialised care is required to maintain good cardiac condition (5, 6). ACHD is classified into three categories according to the 2018 American Heart Association (AHA) guidelines: simple, moderate and complex (7). Moderate and complex CHD in particular have an increased risk of morbidity and mortality (8). Currently, the vast majority of mortality is cardiac in cause and mostly CHD related, except for milder lesions (8). The most common causes of death are heart failure, sudden death (mainly due to arrhythmia) and operative death at time of surgical reintervention (8). The most common atrial arrhythmia in ACHD is intra-atrial re-entry tachycardia (9). Excess mortality in ACHD compared to the general population has been demonstrated (10). As coronary artery disease, arrhythmias and heart failure have become the main focus for the cardiologist, specialised care for ACHD has been campaigned for (2).

The estimated prevalence of CHD at birth was 0.8% after a study examined incidences reported in 62 studies (11). In Sweden, about 1000 children are born annually with heart defects and there is an approximate population of 40,000 adults with CHD (2015), according to a national register for congenital heart defects in Sweden, SWEDCON (12).

> "The challenge is great; the rewards are enormous. For me there have been few things in life which have been more satisfying than to face a small child, struggling for his very existence, to perform some corrective surgical maneuver, and later to see the youngster, thriving and healthy, starting out in life, sound in body and mind".
>
> Richard Edward Gross (1905-1988)
>
> "Father of cardiac surgery"

A systemic right ventricle

TGA and congenitally corrected TGA (ccTGA) are two conditions with a systemic right ventricle. The condition is a ventriculoarterial discordance with an aorta arising from a morphological right ventricle and the pulmonary artery from the morphological left ventricle. In ccTGA, there is also an atrioventricular discordance (13). Before the arterial switch operation was introduced in 1975, patients with TGA were treated with the Mustard or Senning procedure, also referred to as the atrial switch operation. The Senning procedure was named after the Swedish cardiac surgeon Åke Senning (1915-2000), also known for implanting the first cardiac pacemaker (Figure 1) (14).

The Senning procedure was, however, not curative, leaving the right ventricle systemic. Lifelong annual follow-up is indicated due to the risk of serious complications, such as right ventricular failure, arrhythmia, tricuspid valve regurgitation and sudden death (15). The development of systemic right ventricular failure with age is very common in patients after ccTGA, and it has been reported that as many as two-thirds of patients with ccTGA suffer heart failure by the age of 45 years (10). Assessment of the systemic ventricle is thus key in follow-up. Patients with ccTGA die too early from congestive heart failure and sudden death. It is reported that only 50% of patients with associated lesions were alive at the age of 40 years; without associated lesions 50% of patients were alive at the age of 60 years (16).

Use of echocardiography is essential in follow up and may be a challenge since right ventricle systemic size and function require a CHD echocardiographer (Figure 2). CMR is recommended to quantify ventricular volumes and ejection fraction, especially since echocardiographic assessment of systolic function in a systemic right ventricle may be difficult and less reliable. CMR is optimal, however, it can be incompatible in patients with pacemakers. The insertion of a pacemaker is very common since complete atrioventricular (AV) block is a common late complication with a 2% loss of AV conduction per year (16).

SWEDCON

SWEDCON – the SWEDish registry of CONgenital heart disease is a Swedish national registry for data on patients with CHD. The register was created in the early 1990s and, by 2009, started to develop paediatric and surgical sections. The registry consists of four sections: foetal heart diagnosis, paediatric cardiology, adult congenital heart disease and congenital heart surgery (17).

The registry contains information such as clinical condition, echocardiography results, blood tests, surgeries and catheter interventions. The overall coverage rate by SWEDCON is 84% of all the hospitals in Sweden (18).

In 2017, a validation study was performed to assess data registered in two of the main parts of SWEDCON against the data registered in the patients' medical records. The concordance between data regarding medical treatment in SWEDCON and medical records was 86-100% with a specificity of 86-100% and a sensitivity of 50-100%. The concordance between SWEDCON and medical records for performed examinations was 87-100% with a specificity of 100% for most data (17).

AuriculA

AuriculA is a Swedish national quality registry for atrial fibrillation (AF) and anticoagulation. The registry was founded in 2006. The registry is used for patient characteristics, follow-up, dosage control of warfarin, indications, concurrent illnesses and complications. By 2008, 16,000 patients and 225,000 INR values were registered. Routine follow-up telephone calls are used to register complications prospectively (19).

AuriculA has a separate part with the purpose of recommending dosing for anticoagulation treatment. The dosing programme suggests the dosage of warfarin according to an algorithm based on the two last measured INR values (19).

In an evaluation study of the anticoagulation control in Sweden, a high quality of anticoagulation therapy was found, with the author proposing use of the AuriculA dosing programme as a contributing factor to the results (19).

Thromboembolism

TE is one of the most feared complications in ACHD with an increased risk with cerebral infarction being the most common manifestation of TE (20-22). The ACHD group has been described as facing a 10-to-100-fold higher risk of thromboembolic

events compared to age-matched controls (11). The ischaemic stroke rate in ACHD was determined as 0.5-1% per year of follow-up, 9-12 times higher in patients below 55 years of age than in matched controls (22). Haemorrhagic stroke rates were 5-6 times higher in the same age group. Studies on thromboembolic and major bleeding events in ACHD are scarce. According to the Euro Heart Survey which included 4000 patients, the stroke incidence (including transient ischaemic attacks) was estimated to be 4% (23). Data from two large ACHD registries estimated TE to account for 14% of deaths (24-26).

Risk factors and assessment

Risk factors for TE have been studied in different cohorts with varied results. Risk has been related to CHD type and complexity (3,4). Multiple factors may increase the risk of TE. Erythrocytosis which can develop due to chronic cyanosis in cyanotic CHD may induce hyperviscosity, associated with increased risk of thromboembolic events and bleeding (11). Interventional sites, frequent catheterisation and residual lesions are also related to increased risk of thrombosis (16-19). Thrombocytopenia, platelet function abnormalities, decreased production of coagulation factors secondary to impaired liver function and vitamin K deficiency and primary fibrinolysis have all been described in erythrocytosis (12-15). From four studies on ACHD, three reported atrial arrhythmias as a risk factor and diabetes in two studies (21, 22, 27, 28). Other important risk factors, reported in the above-mentioned studies, for thromboembolic complications are diabetes mellitus, hypertension, cardiac surgery and recent myocardial infarction.

In AF, the CHA_2DS_2-VASc composite score (Congestive heart failure, Hypertension, Age ≥ 75 years [Doubled], Diabetes, Stroke/transient ischaemic attack/thromboembolism [Doubled] — Vascular disease, Age 65—74 years and Sex category [Female]) is used to estimate an annual thromboembolic risk (29). The applicability of the score to the ACHD population has not been proven. A Japanese study demonstrated that thromboembolic events occurred even in ACHD patients with a low or intermediate risk score (30). In a retrospective North American study involving 12 centres and 482 patients, neither the $CHADS_2$ or the CHA_2DS_2-VASc scores were predictive of thromboembolic event risk and severe CHD complexity was the only risk factor associated independently with thromboembolic events (31). CHD complexity was proposed to be included in the CHA_2DS_2-VASc score. However, this did not adequately predict residual thromboembolic event risk in the study model. Conclusively, as scoring for risk stratification is not available, certain risk factors should be considered when deciding upon initiation of anticoagulation treatment.

Bleeding risk

Anticoagulation treatment in ACHD was independently associated with a 4-fold higher risk of bleeding (31). The HAS-BLED score is used to assess the risk of bleeding before initiation of anticoagulation therapy (32). The score assigns 1 point for the presence of each of the following bleeding risk factors: hypertension (H), abnormal renal and/or liver function (A), previous stroke (S), bleeding history (B), labile INR (L), elderly (E) and concomitant drugs and/or alcohol excess (D). A score ≥ 3 indicates a high risk of bleeding, especially intracranial haemorrhage (32). Khairy et al reported an association between major bleedings and the HAS-BLED score in a retrospective multicentre ACHD cohort (31). No association was found between CHD complexity and major bleedings.

Diagnostics

Echocardiography and magnetic resonance imaging

Inge Edler, a cardiologist, and Hellmuth Hertz, a physicist in Lund, Sweden were the first ones to document the performance of what resembles transthoracic echocardiography (TTE). The method was developed primarily for the assessment of mitral stenosis (2,3). The method was later developed using the time-motion or motion-mode (M-mode) approach. The Doppler technique was developed by Shigeo Satumora in 1955 (33). Since that time, modes such as A-mode, 2-dimensional and 3D have been developed.

In ACHD it is possible to use echocardiography to diagnose cardiac anatomy, situs of the heart, the atria and ventricles, heart valves, and connection of the heart to the great arteries. The anatomy and function of cardiac valves may be evaluated with TTE and transoesophageal echocardiography (TEE) with or without 3D. 3D echocardiography can be useful in the evaluation of the shape, size and the surrounding structures of different defects. Ventricular size, ejection fraction, volume overload or pressure overload, can all be evaluated using TTE. Tissue Doppler imaging, longitudinal strain and strain rate may also be used in function evaluation. To assist in the imaging evaluation of ACHD, recommendations for echocardiography according to defects have been put together by The International Society for Adult Congenital Heart Disease (ISACHD) (34).

The assessment of the right ventricle by echocardiography can be difficult (35). Additional imaging may be needed, and CMR is regarded as the gold standard in assessment of right ventricle volumes, size, morphology, and function.

Not only is it recommended to evaluate the right ventricle with CMR in ACHD, but also the systemic and pulmonary veins, collaterals and arteriovenous malformations, quantification of shunts (Qp:Qs), distribution to the right/left lung and evaluation of myocardial fibrosis/scars and more (16). The lack of radiation makes CMR useful in follow ups when frequent measurements are needed, such as aortic dimensions measurements. However, there are some limitations with CMR such as availability, and relative contradiction in patients with pacemakers and implantable cardioverter-defibrillators.

In a study comparing the diagnostic value of TEE and magnetic resonance imaging with that of TTE in the evaluation of ACHD, the two first methods were found to

be beneficial complementary imaging techniques and a combination of all three was recommended in complex cardiac defects (36).

Biomarkers

Natriuretic peptides B-type natriuretic peptide (BNP) and NT-proBNP have been shown to be useful in risk stratification in ACHD patients (37).

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing of exercise capacity (peak oxygen consumption), ventilation to carbon dioxide output (VE/VCO_2) slope, heart rate, blood pressure**,** arrhythmias and desaturation evaluates in an objective manner functional capacity and physical fitness. These have been shown to be correlated with morbidity and mortality in ACHD patients (38). Serial exercise testing is used in long-term follow-up, timing of interventions and reinterventions and is useful for individualised exercise prescription (39).

Time in therapeutic range

The stroke-risk reduction is dependent on a therapeutic anticoagulation therapy. TTR is a measure of the quality of anticoagulation therapy and reflects the percentage of which the patients' INR is in a therapeutic range. TTR is used as a marker for the quality of anticoagulation therapy.

TTR is calculated according to Rosendaal's method (40), which uses linear interpolation to assign INR values between successive observed INR values. In patients with AF, TTR was one of the most widely used measures to determine INR control (41). A lower TTR increases the risk of TE and bleeding events.

INR variability

Whereas TTR evaluates the time in therapeutic range, INR variability describes the variation or fluctuation of the INR values, regardless of whether the values are in the therapeutic range. The marker has been shown to predict definitive outcomes (42-44) and predicting adverse events independent of TTR (44).

INR variability is calculated using Fihn's method (42), which is similar to the formula of standard deviation (SD).

Anticoagulants and treatment in ACHD

Warfarin was discovered by Karl Link in 1933 in an attempt to develop an effective rat poison. In 1954, the substance was approved for medical use (45). Warfarin is a VKA, blocking vitamin K epoxide reductase, which is needed for the synthesis of vitamin K-dependent coagulation factors (II, VII, IX and X) (46). The effect is later measured with INR values, aiming for a certain therapeutic range. Due to this, regular monitoring and dose adjustment is required. The dosing can be difficult, as interactions and factors such as concomitant medications, dietary vitamin K, alcohol and genetic polymorphism influence the metabolism of warfarin (47, 48). In nonvalvular AF, warfarin reduces ischaemic stroke risk by two-thirds (49).

NOAC, such as apixaban, dabigatran, rivaroxaban and edoxaban, do not exhibit the same interactions with concomitant medications or diet and do not require frequent monitoring and/or dose-adjustments. Apixaban, edoxaban and rivaroxaban are factor Xa inhibitors, whereas dabigatran is a direct thrombin inhibitor (50). In 2021 in a comparison of NOAC to warfarin in patients with AF and valvular heart disease, a systemic review and meta-analysis found the efficacy and safety of NOAC as a thromboprophylactic to be similar to that of warfarin (51).

Warfarin has been the primary choice for ACHD as it was the first oral anticoagulant to be introduced, with NOAC thereafter successively and slowly becoming an alternative with growing use. Results from a nationwide German retrospective study which included more than 44,000 patients showed NOACs to be associated with an increased risk of major adverse cardiovascular events and mortality, suggesting further prospective studies (52). An international multinational prospective study on NOACs in ACHD, including 530 patients with a median follow-up of 1 year, indicated that NOACs were safe and may be effective for thromboembolic prevention in adults with heterogenous forms of congenital heart disease (53).

Materials and Methods

Paper I

The study group consisted of 11 patients. Patients with a systemic right ventricle, specifically TGA and ccTGA patients, were identified in SWEDCON. Patients without CMR data were excluded. Further criteria were: 2) data from other parameters to be collected within the time span of 1 year, 3) adequate echo-cardiographic image quality, and 4) patients had reached their teens at the time of data collection. Other parameters included were NT-proBNP levels, NYHA-class (I-IV), exercise test performance and the results of CMR and TTE loop examination.

Paper II and Paper III

The study population consisted of 213 patients. Primarily, ACHD with a registered use of oral VKA in the South Region of Sweden, were identified using SWEDCON (n=424). AuriculA was used to access anticoagulation data such as INR values and indications, resulting in a total of 218 patients (Figure 1). No statistically significant difference was found comparing age (mean 48 years) and gender (55% male) to 120 of the unlinked patients. Patients with INR values over 3 months were included and with a minimal age of 15 years, resulting in the exclusion of five patients. The earliest INR data were from the year 2007. Oral anticoagulation indications were grouped into valvular and non-valvular, including AF and venous thromboembolism (VTE). If both a valvular and non-valvular indication were present, the valvular indication was considered primary. INR variability was calculated using Fihn's method (54) and TTR with Rosendaal's method (40). TTR aim was determined by indication according to recommendations: INR 2-3 for all patients except for patients with one mechanical mitral valve or two mechanical valves for whom the aim of INR was 2.5-3.5 (55). For TTR the NICE definition of good anticoagulation control was used: >65% (56). Congenital heart defects were classified into simple, moderate and complex according to guidelines (7). In the analysis, the groups were divided into simple-moderate and complex, as only complex CHD (congenital heart defect) has been associated with TE risk (31).

Data on primary endpoints, clinically verified arterial or venous thrombosis and major bleeding events according to ISTH (International Society on Thrombosis and Haemostasis) definitions recorded prospectively and which are requested annually

and at the end of each treatment period, were provided by AuriculA (57, 58). The register data in regard to anticoagulantion therapy retained was quality controlled by a second confirmation of medical journals within the current study. The major bleedings were divided into three locations: intracranial, gastrointestinal or other/unspecified bleeds. The TE events were divided into stroke/transient ischemic attack (TIA) or peripheral TE.

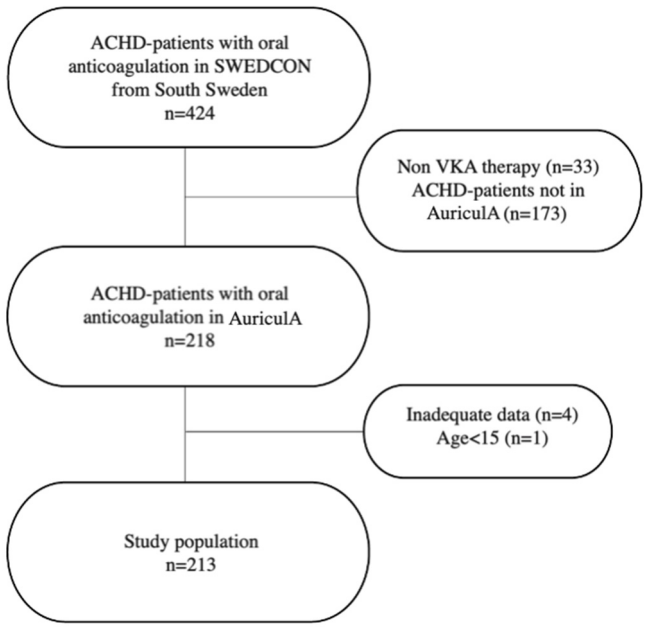

Figure 1. Number of patients recruited from SWEDCON and AuriculA registries.

Paper IV

SWEDCON was used to identify retrospectively all ACHD patients in the South Region of Sweden with a registered use of oral anticoagulation (n=424). AuriculA was used in the next stage to identify all patients who had taken NOAC therapy (n=33). A minimal therapy of 3 months was set as an inclusion criterion; one patient was excluded. Two patients were excluded for being duplicates, resulting in a total study population of 30 patients.

Gender, age, data on anticoagulation and complications were provided by AuriculA. SWEDCON provided the main congenital heart defect diagnosis, comorbidities and interventions. Medical records of the patients were also reviewed for diagnoses and events. CHA_2DS_2-VASc and HAS-BLED scores for the calculation of atrial fibrillation stroke risk were calculated at the time of each NOAC initiation. Start

and stop date of anticoagulation therapy in the patient's medical record also determined the duration of therapy. Congenital heart defects were classified into simple, moderate and complex according to guidelines (7).

Complications registered by AuriculA were according to ISTH (International Society on Thrombosis and Haemostasis) definitions for major bleeding and clinically verified arterial or venous thrombosis (57, 58). Minor bleedings were not searched for due to unreliable accessibility in medical journals. The register data in regard to anticoagulantion therapy retained was quality controlled by a second confirmation of medical journals within the current study. The major bleedings were divided into three locations: intracranial, gastrointestinal or other/unspecified bleeds. The TE events were divided into stroke/transient ischemic attack (TIA) or peripheral TE.

Statistical analysis

In all the papers, a p-value of less than 0.05 was considered statistically significant. The analyses were conducted using IBM SPSS Version 24.

Paper I

Continuous data are presented as the median and range. NT-proBNP was not distributed normally and therefore was log transformed. The relationship between the systemic right ventricle ejection fraction derived from CMR, and exercise test results, logNT-proBNP, and echocardiographic parameters (global longitudinal strain [GLS], tricuspid annular plane systolic excursion [TAPSE], fractional area change [FAC], apical 4 chamber [AP4] and basal short axis [SAX]) was evaluated using the Pearson correlation coefficient. The relationship between NYHA class and the systemic right ventricle ejection fraction, exercise test results, logNT-proBNP, and echocardiographic parameters (GLS, TAPSE, FAC, AP4 and SAX) was evaluated using the Spearman correlation coefficient.

Paper II

Descriptive statistics were reported as counts, percentages, means and medians, depending on whether there was normal distribution. Due to skewness, INR variability was transformed logarithmically. For logINR the cut-off of >0.41 for high variability was used after dichotomising logINR values. Binary logistic regression was used to calculate odds ratios (OR) for potential predictors. Univariate analysis was made for all covariates as independent factors. Covariates with a prevalence rate of <5%, i.e. history of bleeding, liver failure, vascular disease and alcohol overconsumption, were not included in the analysis. TTR and logINR were dependent factors in the analysis. Multivariate logistic regression analysis was used to identify predictors of good TTR and low INR variability. The multivariate analysis model was formulated adjusting covariates identified from the literature, such as age, gender, heart function and duration of treatment (59-62). For comparing means, independent samples *t*-test Chi-squared analysis was used. Pearson correlation coefficient was used for bivariate correlation analysis.

Paper III

Descriptive statistics were reported as counts, percentages, means and medians depending on distribution. For data on anticoagulation, mean, SD, median, interquartile range (IQR) and percentiles were used as distribution varied for the variables. Due to skewness, INR variability was transformed logarithmically for improved analysis. Values of logINR were dichotomised based on the median value and used as a cut-off value for defining low/high. For logINR, the cut-off value of >0.41 for high variability was used after dichotomising logINR values. Incidence rates were expressed as number of events per person-time with corresponding 95% confidence intervals (CI). Univariate analysis was performed for all covariates as independent factors. Covariates with a prevalence rate of <5%, i.e. history of bleeding, liver failure, vascular disease and alcohol overconsumption, were not included in the analysis. Congenital heart defects were classified into simple, moderate and complex according to guidelines (7). In the analysis, the groups were divided into simple-moderate and complex, as only complex CHD (congenital heart defect) has been associated with TE risk (63).

Multivariate logistic regression was used to identify risk factors associated with complications. In this analysis, risk factors reported in the literature were included. The study population was not divided into subgroups, as cases in each group would be too few. Cox proportional-hazard regression models for survival analysis, using time since start of anticoagulation therapy as the time variable, were used to estimate hazard ratios.

Paper IV

Descriptive statistics were used to summarise characteristics. Results were presented as median with SD or IQR, percentages and 95% CI. Calculations and analyses were performed using SPSS Statistics Version 25 and Microsoft Excel Version 15.41.

Results

Paper I

A total of 11 patients were included in the study according to the inclusion criteria. Seven were recruited after atrial switch operation and four with ccTGA. The patient characteristics and measured parameters are given in Table 1. One of the atrial switch operations was the Mustard procedure and the other six were Senning procedures. None of the ccTGA had undergone previous surgery. Moderate tricuspid regurgitation was seen in two patients after atrial switch operation.

The median age of the patients with ccTGA was 35 years (25-67 years), and that of the patients undergoing atrial switch operation was 30 years (13-37 years) (Table 1). Seven patients were classified as NYHA class I, three as class II and none in the other classes. The venous left ventricular ejection fraction (LVEF) derived from echocardiography was 41% (34-47%) in patients who had undergone atrial switch operation and 40% (27-40%) in ccTGA patients. The right ventricular ejection fraction (RVEF) derived from CMR was 44% (32-60%) in patients who had undergone atrial switch operation and 48% (23-60%) in ccTGA patients (Table 1). The median level of NT-proBNP was 382 ng/L (75-2537 ng/L) (Table 1).

Table 1. Patient characteristics and descriptive statistics.

	After atrial switch operation	ccTGA	Total
Patients (n)	7	4	11
Male/Female (n)	7/0	2/2	9/2
Age (years)	30 (13-37)	35 (25-67)	32 (13-67)
History of clinical arrhythmia (%)	86	50	73
Moderate TR (n)	2	0	1
VSD-closure (n)	0	0	0
NYHA class (n)			
I	5	2	7
II	2	1	3
III	0	0	0
IV	0	0	0
CMR-RVEF (%)	44 (32-60)	48 (23- 59)	44(23 – 60)
Echocardiographic parameters			
GLS (%)	-12.4 (-19.1- -11.0)	-14.6 (-23.8- -7.8)	-13.6 (-23.8 - -7.8)
TAPSE (mm)	17.0 (12.5-18.0)	15.6 (14.3- 16.9)	16.9 (12.5- 18.0)
AP4 (%)	14.3 (11.3-18.3)	15.5 (7.8-19.3)	14.6 (7.8-19.3)
FAC (%)	0.22 (0.18- 0.37)	0.24 (0.21-0.28)	0.22 (0.18 – 0.37)
SAX (%)	8.0 (3.5-15.8)	19.8	11.0 (3.5- 19.8)
LVEF (%)	41 (34-47)	40 (27-40)	40.5 (27-47)
NT-pro BNP (ng/L)	231 (75-1349)	1591 (250-3537)	382 (75-2537)
Exercise stress test			
Max. heart rate (bpm)	162 (109-176)	179 (163-184)	170 (109-184)
Max. SBP (mmHg)	170 (125-195)	170 (120-170)	170 (120-195)
Max. working capacity (W)	170 (105-225)	210 (106-218)	180 (105-225)
Expected max. working capacity (%)	66 (43-89)	87 (86-87)	71 (43-89)

Table 2 gives the correlation coefficients and p-values. A statistically significant correlation was found between CMR-derived RVEF and right ventricular GLS (r=-0.627; p=0.039) (Figure 3). No correlation was found between the CMR-derived RVEF and any of the other echocardiographic parameters. The median maximum working capacity in patients after the atrial switch operation was 170W (105-225W) and in the ccTGA patients was 210W (106-218W). No correlations were found between the CMR-derived RVEF and the exercise test parameters. No statistically significant correlation was found between CMR-derived RVEF and logNT-proBNP or NYHA class.

Table 2. Correlation coefficients for CMR-derived right ventricular ejection fraction (RVEF) and given parameters

Parameters	RVEF	
	r-value	p-value
Max. heart rate	0.14	0.70
Max. SBP	0.26	0.48
Max. working capacity	0.60	0.07
Expected max. working capacity	0.47	0.21
logNT-proBNP	-0.615	0.078
NYHA class	-0.114	0.754
GLS	-0.63	0.04
TAPSE	-0.11	0.86
AP4	0.56	0.08
FAC	-0.11	0.74
SAX	0.60	0.27

Paper II

The total study population consisted of 213 patients slightly male dominated (58%) with an overall mean age of 50 years. Five patients with INR data <3 months or age <15 years were excluded. The most common congenital heart diseases were atrial septal defect (ASD) (26%), followed by bicuspid aortic valve (10%) and coarctation of the aorta (10%). The indication for VKA therapy was mostly non-valvular (59%). The majority of patients (89%) had undergone an intervention, mainly open-heart surgery (73%), while only relatively few had undergone cardiac catheter interventions (15%). The most common co-morbidity was AF (49%), followed by heart failure (33.3%), hypertension (27.2%), anaemia (21.1%), history of TE (17.4%), thrombocytopenia (14.1%), kidney failure (12.2%), diabetes and antiplatelet treatment (6%).

The median duration of therapy was 6.8 years (IQR 5.7) with the lowest duration being 0.25 years. The TTR was distributed normally with a mean of 70.8% and 25th percentile of 61.9% (Figure 2a). The range of TTR was 18.8–96.3%. Mean TTR was 63.7% and 64.7% for the non-valve group and valve-group, respectively. The median INR variability was 0.4 with a 25th percentile of 0.25. The overall mean INR was 2.6 for the study population. For TTR and logINR variability there was no significant difference for subgroup analysis, non-valve versus valve indication ($p>0.1$). However, for the valve group, the mean INR was significantly higher compared to the non-valve group ($p<0.001$): 2.8 versus 2.5, respectively. The correlation coefficient between TTR and logINR variability was $r = -0.6$, $p < 0.01$. The correlation between TTR and INR-variability was $r^2 = 0.38$ (Figure 2b).

Only duration of treatment was a significant predictor of good TTR in the univariate analysis: OR 1.19 (95% CI: 1.08–1.3). Age, female gender, heart failure and duration of treatment were significant in the multivariate analysis with female

gender and heart failure predicting poor TTR (Table 3). The univariate analysis for logINR variability only showed heart failure as a predictor of high logINR variability. In the multivariate analysis with age, gender and duration of treatment, heart failure was also the single significant predictor: OR 1.89 (95% CI: 1.04–3.4, p=0.037).

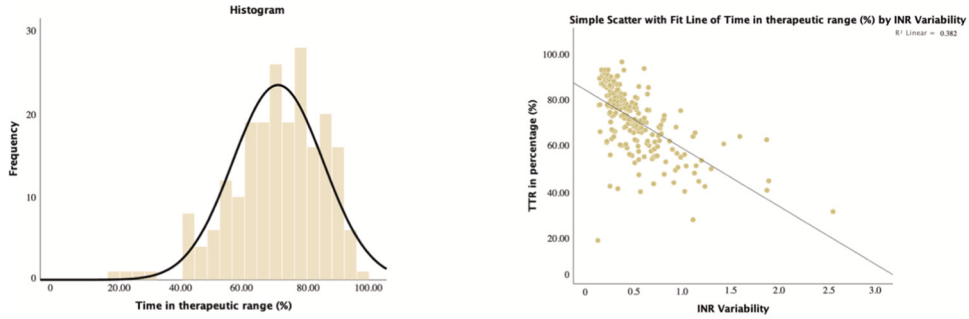

Figure 2. a) Frequencies of time in therapeutic range (%). b) Scatter plot of time in therapeutic range (%) and international normalized ratio (INR) variability.

Table 3. Univariate and multivariate analysis: independent predictors of good anticoagulation control (TTR>65%). OR = odds ratio; CI = confidence interval.

	OR	95% CI	p-Value
Univariate			
Age	1.01	1.00–1.03	0.13
Female gender	0.65	0.36–1.16	0.14
Heart failure	0.59	0.32–1.09	0.09
Kidney failure	0.87	0.42–1.82	0.71
Diabetes	1.54	0.41–5.82	0.52
Hypertension	1.21	0.61–2.40	0.59
Anemia	0.54	0.27–1.06	0.07
History of TE	1.02	0.47–2.20	0.96
Duration of treatment	1.19	1.08–1.30	<0.001
Thrombocytopenia	1.08	0.46–2.50	0.86
Antiplatelet treatment	0.42	0.13–1.34	0.14
Multivariate			
Age	1.02	1.00–1.04	0.019
Female gender	0.51	0.26–0.99	0.048
Heart failure	0.52	0.27–0.99	0.049
Duration of treatment	1.22	1.09–1.30	<0.001

Paper III

Patient characteristics

The study population consisted of 213 patients with an overall mean age of 50 years (Table 4). Gender was slightly male dominated (58%). No statistically significant difference was found comparing age (mean 48 years) and gender (55% male) to the unlinked group (120 patients). The most common congenital heart disease was atrial septal defect (ASD) (26%), followed by bicuspid aortic valve (10%) and coarctation of the aorta (10%) (Table 5). Overall, 83% of patients had simple-moderate congenital heart disease and 16% had complex disease (Table 5). The indication for VKA therapy was valvular (41%) and 59% non-valvular, with TE recorded in 12% (Table 4). The majority of the patients in our study (89%) had undergone an intervention, mainly open-heart surgery (73%), while only relatively few had undergone cardiac catheter interventions (15%).

Quality of anticoagulation therapy

The mean follow-up time was 6.6 years (± 3.3 years) with the lowest duration being 0.25 years (Table 6) and a total cumulative time of 1411 patient-years. The mean TTR was 70.8% and a 25^{th} percentile of 61.9% (Table 6). The median INR variability was 0.4 with a 25^{th} percentile of 0.25 and overall mean INR of 2.6 for the study population. For TTR and logINR variability, there was no significant difference for subgroup analysis, non-valve versus valve indication ($p>0.1$). However, for the valve group, the mean INR was significantly higher compared to the non-valve group ($p<0.001$): 2.8 versus 2.5, respectively. The correlation between TTR and logINR variability was $r = -0.6$, $p<0.01$. The mean TTR was significantly higher in the group without complications, 71.7% versus 66.4% ($p=0.04$) (Figure 3). The mean logINR-variability was significantly lower in the group without complications ($p=0.01$).

Thromboembolism and major bleeding

Thirty-four complications were registered during the total of 1410 treatment years, including TE and major bleeding events (Table 7). The total incidence rate for complications was 2.4 (95% CI: 1.7-3.4) per 100 patient-years. Fourteen TE events were reported during the follow-up time, with peripheral TE more common than stroke/transient ischaemic attack (TIA) (Table 7). For major bleedings, other bleeds (n=10) dominated, followed by cerebral bleedings (n=10) and gastrointestinal bleedings (n=4), a total of 20 bleeding events. No recurrent bleedings were registered. The incidence of TE and major bleedings was 1.0 (95% CI: 0.6-1.6) and 1.4 (95% CI: 0.9-2.2) per 100 patient years, respectively (Table 7).

Regarding comorbidities, four patients had coagulopathies (one with TE, three with major bleeding), three patients had cancer diagnosis (one TE, two major bleeding), two patients had alcohol abuse (major bleeding), one attempted suicide (major bleeding) and one had mental health difficulties (major bleeding). Two of the cerebral bleedings were traumatic. The incidence per 100 patient-years was significantly lower in patients with good TTR 2.1 (95% CI: 1.2-3.4, $p<0.05$) than those with poor TTR 3.7 (95% CI: 2.4-5.6). Comparing the incidence in high and low INR variability, the difference was not significant, although the incidence per 100 patient-years was lower in the low INR-variability group: 2.2 (95% CI: 1.2-3.6) ($p=0.08$), compared to 3.5 (95% CI: 2.2-5.2) in the high INR variability group. History of TE was the sole significant risk factor for complications with an OR of 3.53 (95% CI: 1.33-9.37) (Table 8).

Mortality

A total of 43 patients died during the observed time of the study. The all-cause mortality rate was 3.1 per 100 patient-years (95% CI: 2.2-4.1). The mean age of these patients (62.8 years ± SD 29.5 years) was higher than the mean age of the total study population. Cardiac-related cause of death including valve-related was most common (48.7%), followed by other (35.6%), intracerebral bleeding (5.1%), other bleeding (2.5%) and unknown (7.7.%). Age and hypertension were significant predictors of mortality using multivariate Cox regression as presented in Table 9.

Table 4. Study population characteristics.

	n (%)
All patients	213 (100)
Age (years)	53* (± 18)
Male	125 (58)
Valve indication	87 (41)
AVR **MVR** **AVR** **MVR**	63 (30) 19 (9) 1 (1)
Valve annuloplasty	4 (2)
Non-valve indication	126 (60)
Atrial fibrillation	104 (49)
Thrombosis indication	25 (12)
Hypertension	58 (27)
Diabetes	13 (6)
Vascular disease	10 (5)
Prior stroke/transient ischemic attack	36 (17)
Prior major bleeding	3 (1)
Systemic ventricular function (EF %)	
>50	136 (64)
35-50	45 (21)
<35	26 (12)
Renal function (eGFR, mL/min/1.73 m^2)	
>90	65 (30)
60-89	92 (43)
30-59	23 (11)
15-29	3 (1)
eGFR	76 (± 20)
Liver failure	8 (4)
Alcohol overconsumption	2 (1)

Table 5. Congenital heart disease (CHD) diagnoses and interventions.

	Main diagnosis	**Secondary and tertiary diagnosis**
Congenital heart disease	***n* (%)**	***n* (%)**
ASD	55 (25.8)	15 (7.0)
Bicuspid aortic valve	22 (10.3)	16 (7.5)
Coarctation of the aorta	22 (10.3)	3 (1.4)
Aortic valve stenosis and **insufficiency**	14 (6.5)	1 (0.5)
Tetralogy of Fallot	12 (5.6)	0
VSD	11 (5.2)	22 (10.3)
TGA	10 (4.7)	1 (0.5)
CCTGA	8 (3.7)	16 (7.5)
Ebstein anomaly	9 (4.2)	0
Mitral or tricuspidal valve defect	8 (3.8)	6 (2.8)
Patent foramen ovale	8 (3.8)	1 (0.5)
Single ventricle	7 (3.3)	0
Marfan's syndrome	7 (3.2)	0
AV commune	5 (2.3)	1 (0.5)
Dilated aortic ascendens	3 (1.4)	17 (8.0)

Table 5. Congenital heart disease (CHD) diagnoses and interventions.

Pulmonary vein or artery defect	3 (1.4)	11 (5.2)
Patent ductus arteriosus	2 (0.9)	8 (3.8)
Truncus (type 1 & 2)	2 (0.9)	0
Cor triatriutum	1 (0.5)	0
Coronary artery aneurysm	1 (0.5)	0
Hypertrophic cardiomyopathy	1 (0.5)	
Hypoplastic left ventricle	1 (0.5)	
Congenital Complete AV-block	1 (0.5)	
Eisenmenger syndrome	0	3 (1.4)
Severity of defect		
- Simple-moderate	178 (84%)	
- Complex	34 (16%)	
Intervention	***n* (%)**	
No intervention	23 (11)	
Open surgery	158 (74)	
- **1 procedure**	50 (24)	
- **2 procedure**	51 (24)	
- **>2 procedures**	57 (27)	

Table 6. Descriptive statistics of anticoagulation measurements.

	Mean (± SD)	Median	IQR	25th percentile	75th percentile
TTR	70.8 (± 14.2)	71.9	19.8	61.9	81.6
INR variability	0.5 (± 0.4)	0.4	0.4	0.3	0.6
Mean INR	2.6 (± 0.4)	2.5	0.3	2.4	2.7
Tests in range	64.4 (±12.6)	65.5	67.1	55.0	73.7
Duration (years)	6.6 (±3.3)	6.8	5.7	3.7	9.5

Table 7. Incidence of thromboembolism and major bleedings.

Incidence*: per 100 patient-years (95% CI).

	Absolute incidence	Incidence*
Stroke/TIA	6	0.4 (0.2-0.9)
Peripheral TE	8	0.6 (0.3-1.1)
All TE	14	1.0 (0.6-1.6)
Cerebral bleeding	6	0.4 (0.2-0.9)
Gastrointestinal bleeding	4	0.3 (1.0-0.7)
Other	10	0.7 (0.4-1.3)
All major bleeds	20	1.4 (0.9-2.2)
All adverse events	34	2.4 (1.7-3.4)

Table 8. Independent risk factors for complications (thromboembolism and major bleedings combined).

	p-value, univariate	*p*-value, multivariate	Odds ratio (95% CI)
Age	0.10	0.55	1.01 (0.98-1.04)
Female sex	0.01	0.06	2.29 (0.97-5.41)
Heart failure	0.22	0.50	1.37 (0.55-3.44)
Kidney failure	0.02	0.18	2.20 (0.70-6.58)
Diabetes	0.35	0.17	0.20 (0.02-2.00)
Hypertension	0.74	0.60	0.77 (0.28-2.10)
History of TE	<0.01	0.02	3.28 (1.23-8.78)
TTR>65%	0.09	0.94	0.95 (0.30-3.03)
Low INR variability	0.13	0.26	1.93 (0.61-6.10)
Anemia	0.14		
Duration of treatment	0.20		
Antiplatelet drugs	0.14	0.81	0.81 (0.14-4.68)
Complex CHD	0.93	0.98	0.98 (0.32-3.15)

Table 9. Estimated hazard ratios for all causes of death.

Variables	Hazard ratio	(95% CI)	*p*-value
Age	1.05	1.01-1.09	<0.01
Female	1.07	0.47-2.41	0.88
Hypertension	0.36	0.14-0.97	0.04
Heart failure	1.30	0.55-2.95	0.58
Atrial fibrillation	1.46	0.61-3.51	0.40
Kidney failure	0.39	0.58-4.08	0.39
Diabetes	1.85	0.56-6.12	0.74
Prior stroke/TIA	1.20	0.46-3.12	0.71
Complex CHD	2.72	0.89-8.39	0.08

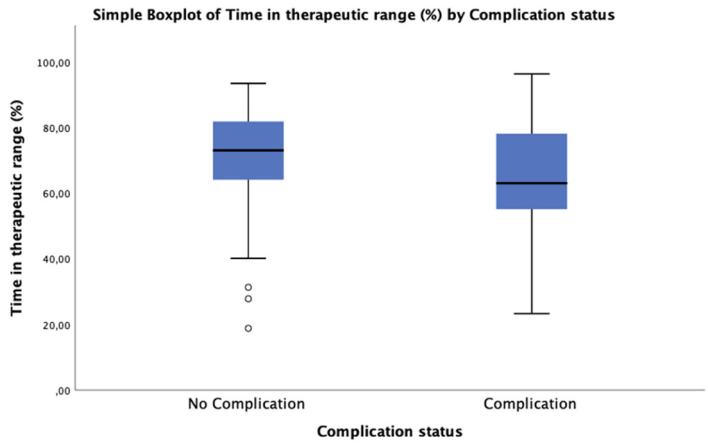

Figure 3. Boxplot of TTR (%) by complication status.

Paper IV

Thirty adults with congenital heart disease were identified with NOAC as the anticoagulation therapy. The median age was 55 years (SD 17 years) with a slight male predominance (57%). The predominant indication was atrial arrhythmia (87%) with five patients also having bioprosthetic valves (Table 10).

Apixaban was the most commonly used NOAC (47%) followed by rivaroxaban (30%) and dabigatran (23%). Severity of the defects was predominantly simple-moderate (67%) with 27% being complex. Hypertension was the most common comorbidity (30%). Median CHA_2DS_2-VASc was 2 points (IQR: 0-3) with 12 patients (40%) having a score higher than the median. The median HAS-BLED score was 1 point (IQR: 0-2), with 57% having a score lower than 2 points. In a total cumulative duration of 63 years of follow up, no thromboembolic events were noted. One major bleeding event was recorded, described as "other", not intracranial or gastric, giving an annual rate of 1.58 (95% CI: 0.08-7.78). The patient concerned was a female, 46 years of age, with Fallot's tetralogy (moderate CHD) who was treated with rivaroxaban. She had a CHA_2DS_2-VASc score of 1 and HAS-BLED score of 0. The bleeding occurred after 19 months of treatment.

The most common cause of discontinued treatment was according to plan (16.7%), followed by a new indication (6.7%) and change to another anticoagulation (6.7%) (Table 11).

Table 10. Demographics, severity of CHD, comorbidities and results of CHA2DS2-VASc and HAS-BLED scores.

Demographics	
All patients (n)	30
Gender	17 male (57%): 13 female (43%)
Median age*	55 years (SD 17 years)
Median duration of therapy (months)	17 (Min-max: 3-71)
Total cumulative duration of therapy (months)	764
Complications	
Events during therapy	1
Thrombotic or thromboembolic events	0
Bleeding events	1
Severity of CHD*	
Simple	9
Moderate	11
Complex	8 (27%)
Unclassified	2
Defect repaired	27 (90%)
Bioprosthetic valves	5
Indication for anticoagulation	
Atrial arrhythmia	26
Venous thromboembolism	1
Other	3
Comorbidities	
Hypertension	9 (30%)
Diabetes	4 (13%)
Type of NOAC	
Apixaban	14
Rivaroxaban	9
Dabigatran	7
Scores	
Median CHA_2DS_2-VASc	2 (IQR: 0-3)
0	8
1	4
2	6
3	10
4	1
5	1
Median HAS-BLED	1 (IQR: 0-2)
0	13
1	4
2	12
3	1

Table 11. Causes for discontinued NOAC treatment.

Causes	**Number (n)**
According to plan	5
Due to bleeding	1
Due to other diseases	1
Due to poor compliance	1
Due to new indication	2
Change to other anticoagulation	2

Discussion

Assessment of the systemic right ventricle

Our study found GLS of the systemic right ventricle as a possible alternative to MRI. The study may thus support the use of the method in the assessment of the systemic right ventricular function. A unique aspect of the study is including echocardiographic parameters, NT-proBNP, NYHA class and performance on exercise stress test, which has not been done before. Using an echocardiographic parameter may simplify the follow-up of patients with ccTGA or after atrial switch operation.

The correlation between CMR-derived right ventricular function and right ventricular GLS was reported earlier (64). This study also found a correlation with fractional area change of the right ventricle, which was not seen in our study. The mean patient age in that study was 25 years, compared to 30 years in our study. The study also found that GLS was able to discriminate between a systemic RVEF below and under 45%. GLS has been found to have a higher predictive value, better measurement-remeasurement reproducibility, and can predict adverse clinical outcomes such as morbidity and mortality (64). The reduced septal longitudinal and circumferential strain has been suggested to contribute to reduced septal work and failure of the systemic right ventricle in TGA patients (65).

For the other studied parameters, our findings had varied similarities. The correlation between right ventricular function and NT-proBNP has been reported in previous studies. Plymen et al. reported a statistically significant correlation between CMR-derived RVEF and NT-proBNP, but not to NYHA class in patients following the Mustard and Senning procedures (66). The absence of a correlation with NYHA class was in line with our findings. Kotaska et al. also reported a relationship between NT-proBNP and the systemic right ventricular systolic function assessed by TTE in adult patients after atrial switch operation (67). In a systemic review on NT-proBNP in complex CHD, a significant correlation between BNP and RV function derived by CMR or echocardiography was reported in five of eight studies (68). In two of the studies of the above-mentioned systematic review, a correlation was also seen between the severity of tricuspid regurgitation and BNP. A possible explanatory factor for our findings may thus be the absence of tricuspid regurgitation in our study group and the non-normal distribution of NT-proBNP.

The exercise parameters did not show a significant correlation with CMR-derived RVEF. Earlier studies have reported incoherent findings on the correlation between systemic right ventricular function, described by CMR and echocardiography-derived RVEF and echocardiographic parameters such as GLS, FAC, TAPSE, and exercise capacity (69-72). In a larger study with 105 patients with a systemic right ventricle, neither CMR- nor echocardiography-derived systolic parameters were correlated to reduced exercise capacity (73).

Quality of anticoagulation

Our study was the first on TTR and INR-variability in ACHD patients, reporting an overall high quality of VKA therapy and confirming earlier reported predicting factors such as age, gender and heart function.

We found a TTR of 71% and INR values in the range of 64%. A multi-centre study on anticoagulation control including 18,391 Swedish patients based on the common cohort used in our study, AuriculA, reported a mean TTR of 76% (19). The quality is therefore by international standards (TTR>65) acceptable (56), but for Swedish standards is lower. The 25th percentile was 62%, implying that 75% of the study population had a TTR above 60%. With a mean INR value in the range of 64%, only 9% of the TTR was due to interpolation, representing a statistically high actual TTR.

For the INR-variability, the median was 0.4, with a 75% percentile of 0.6. For comparison, a standard deviation of the INR was studied in a Swedish study on 19,180 patients with AF (43). The reported standard deviation of INR was 0.86, which, in our study, corresponds to 0.24. The INR variability of our study population could therefore be described as very good.

As both TTR- and INR-variability are predictors of thromboembolic and bleeding events, this should indicate a low risk of these complications. AuriculA, by providing a web-based dosing algorithm and close monitoring, may be an excellent tool to achieve this. It should, however, be borne in mind that an excellent TTR- and INR-variability may theoretically be protective, but a short period of deviating INRs may make the patient susceptible enough to develop a major bleeding or TE, but they may still present with a good TTR- and INR-variability value.

Incidence of thromboembolism and major bleeding

Although Papers II-IV comprised a small patient population, the distribution of gender and the indication for anticoagulation treatment was distributed evenly. Our study group with a non-valvular treatment indication was larger, which could imply

a risk of TE slightly skewed to that group and thus a lower risk of TE (19). The average age of our study group with regard to an ACHD setting is high, as median life expectancy according to a SWEDCON report (12) on ACHD patients was 65 and 55 years for females and males, respectively. Our study population could be described as moderate-to-low risk for TE and major bleeding according to reported risk factors (21, 22, 27, 28). The prevalence of comorbidity was low, with hypertension being the most common disease (27%) followed by diabetes (6%). Most patients (64%) had normal heart function, with 85% having an ejection fraction over 35%. The average renal function was also relatively high with an average estimated glomerular filtration rate of 76 mL/min/1.73m^2 and only three patients had a function of less than 30%. For ACHD patients, the risk of the complications of atrial arrhythmias and TE have been reported in those with severe complex congenital heart disease (63). In the present study, this group of patients with severe complex congenital heart disease only constituted 16% of the total study population.

Another key factor for complication risk assessment is the quality of anticoagulation treatment and organisation of anticoagulation clinics, which was high in this study due to the assistance of AuriculA. Determined by the recognised indicators of TTR and INR variability, the population in Paper III presented with an average good TTR of 71%, a relatively low average INR variability and thus an average good quality of anticoagulation.

The incidence of TE and major bleedings in Paper III was 1% (CI 95%: 0.6-1.6) and 1.4% per treatment year, respectively. Compared to non-ACHD patients treated with VKA, a large Swedish multicentre study reported a frequency of 2.12% (95% CI: 1.99-2.24) and 2.04% (95% CI: 1.92-2.16) per treatment year for TE and major bleeding, respectively. The results were based on 34,851 non-valvular AF patients with an average mean TTR of 68.6%, a mean age of 72.5 years and a mean CHA_2DS_2-VASc (risk score for AF) score of 3.2 (74). For Paper III, the CHA_2DS_2-VASc score was not calculated, as it had not been shown to be applicable in ACHD. It could, however, serve as an indicator of the prevalence of risk factors, which is why it was included in Paper IV. Comparing internationally, a systematic review reported thromboembolic events and major bleeding of 2.5% (IQR: 1.6-3.6) and 2.2% (IQR: 1.7-2.8) per treatment year, respectively (61). For major bleeding, 28 studies were included and 20 for TE events. The TTR, however, ranged from 29% to 75% (41).

The low incidence of TE and major bleedings in our study could therefore be explained by the high quality of anticoagulation therapy and low-risk study population.

The all-cause mortality rate in our study was comparable to that of a Dutch national registry for ACHD with a rate of 1-6.6% per year for age groups between 50-80 years (26). In the mentioned study mortality was studied following 6933 patients

with a follow-up of 24,865 patient years (26) compared to 1411 patient years in our study. Compared to non-ACHD patients treated with VKA, a large Swedish multicenter study including 40 449 patients and a mean age of 73 years, the mortality rate was higher in our study. A possible explanation for the increased rate could be the lower life expectancy in ACHD patients and that the mean age of the patients was 63 years, which is close to the reported life expectancy in this population according to a previously mentioned Swedish national report (12). In the Dutch study, age, gender and severity of defect were predictors of increased mortality. Only age was in common with our findings of predictors of increased mortality. Hypertension, which has been reported as a predictor of mortality (75) had, in our study, a protective relationship with mortality. Possible explanations could be that patients with hypertension were well treated or received closer monitoring.

Risk factors

Knowledge of risk factors for suboptimal anticoagulation, TE and bleeding may be valuable in identifying patients in need of additional monitoring, and choice and suitability of anticoagulation agent.

Results in Paper II on predictors of good anticoagulation control were mainly consistent with those of previous studies, except for age. Female gender has been reported most prevalently in studies as a risk factor for poor TTR, which was also seen in ACHD patients (62). Increasing age was related to a good TTR. Higher age (approximately >70 years) and a poor TTR have been reported previously (61, 62).

Dietary changes, medication non-compliance and drug interactions have been shown to be causes of non-therapeutic INRs in Fontan patients (76). The pharmacology of warfarin is influenced by these factors, but also by genetic influences (47, 48).

Another problem that may affect anticoagulation control is liver disease in Fontan patients ranging from hepatic congestion, severe fibrosis, with signs of portal hypertension to hepatocellular carcinoma (77). Changes in levels of clotting and fibrinolysis factors has also been described in Fontan patients (78). Benefit of anticoagulation, in the absence of strong risk factor for TE, still requires further studies.

In an ACHD setting, we can expect drug interactions, certainly in patients with complex CHD who may be subjected to polypharmacy. A younger population can also be speculated to be associated with medication non-compliance. A contributing factor may be depressive and anxiety symptoms, which were reported to be prevalent in 31% of ACHD patients screened in a German study (79). Alcohol

consumption has also been reported as prevalent in ACHD (62). A more established relationship with health care could also have a role, which we suspect is the explanation behind duration of treatment being a predictor of good TTR. Heart function showed a relationship with both good TTR and low INR variability in our study. A relationship with good TTR was consistent with earlier studies, whereas the relationship with INR variability is, to our knowledge, a new finding. Effects on pharmacokinetics secondary to heart failure complications, such as liver dysfunction and decreased drug absorption from the gastrointestinal tract, could alone be explanatory (80). A study reported marked fluctuations of NT-proBNP as a risk factor for poor TTR control (81).

In Paper III, risk factors were evaluated for TE and major bleeding together, as subgroup analysis would result in too small groups. History of TE was a significant risk factor for complications in our study. The incidence of complications did increase in patients with poor TTR (<65%), but not when comparing low and high INR variability, suggesting that a TTR>65% could also be applicable in ACHD patients. For ACHD patients, CHA_2DS_2-VASc has been seen not to be applicable for assessing the risk of TE, with TE events occurring even with low scores (30, 31). Congestive heart failure, hypertension, age, diabetes mellitus and vascular disease have been reported as risk factors in ACHD patients. The above-mentioned studies did not, however, report unanimous findings (21, 22, 27, 82). For bleedings, HAS-BLED has been reported to be applicable in ACHD patients (31). The risk of a patient with a history of TE having another TE event could have multiple explanations. A history of TE could, for example, be an indicator of a high-risk patient, explained by episodes of low TTR or high INR variability. Factors such as interventional sites, frequent catheterisation and residual lesions, were not included in our study, but are reported risk factors of TE in ACHD patients (83, 84).

The above-mentioned factors may be a reason for considering closer monitoring or choice of non-VKA anticoagulation therapy.

Anticoagulation therapy

In Paper IV no thromboembolic and major bleeding events during a median duration of 17 months of therapy were reported. Our study contributes to the growing evidence of efficacy and safety data specific to NOAC use in ACHD. NOACs demonstrate several advantages such as more predictable pharmacokinetics, fewer drug- and dietary interactions, easier use and a more attractive benefit-risk profile (85). Patients with a mechanical valve, mitral or tricuspid valve stenosis with enlarged and diseased atria, with or without a mitral or tricuspid bioprosthesis and after cardiac surgery (<3 months) have a contraindication to NOAC (85). NOACs for Atrial Tachyarrhythmias in Congenital Heart Disease (NOTE) registry is a

multinational study providing short-term safety data and is expected to deliver longer-term outcomes successively (www.clinicaltrials.gov: NCT02928133). Growing evidence also supports the use of NOACs in patients with CHD, but various forms of valvular heart disease could translate into indications for ACHD patients with isolated valve lesions, such as mitral regurgitation or aortic stenosis.

A systemic review of NOAC use in ACHD patients included three studies with a total number of 766 patients. The annual rate of thromboembolic and major bleeding events was 0.98% (95% CI: 0.51–1.86) and 1.74% (95% CI: 0.86–3.49), respectively. One study included Fontan patients only, reporting a higher annual rate of both events, confirming the increased risk of TE in ACHD patients with complex severity (86). The two largest studies included 530 and 215 patients, not Fontan-exclusive (53, 87). In these studies, the rate of complex severity of ACHD was 40% and 44.2%, and six and two thromboembolic events were registered, respectively. The total patient-years of follow-up was 896.3 years. Compared to the total patient-years of follow-up of 63.7 years in Paper IV, the low incidence of adverse events in our study is plausible. However, compared to the largest included study of 530 patients, the median follow-up was 1 year, compared to 17 months in Paper IV (53). Furthermore, the prevalence of complex ACHD severity, which is a major risk factor for TE (63), was only 27%. CHA_2DS_2-VASc >2 was between 46.4-49.3%, comparable to 40% in our study. For HAS-BLED, however, the scoring differed, with our study having 57% <2 points and the other two studies reporting a higher 87.5-95% <2 points (53, 87). The risk of bleeding could thus be described to be higher in our study group, but the thromboembolic risk was lower with regard to the prevalence of complex severity defects and CHA_2DS_2-VASc scores. The above-mentioned factors together with the lower patient-years of follow-up could be an explanation for the low rates of TE and bleeding. NOAC was mostly discontinued according to plan, a new indication and change to another anticoagulant. Bleeding, other diseases and poor compliance were other less common causes for stopping NOAC therapy.

Data showing the efficacy and safety of NOAC in ACHD are growing, however, NOACs are still insufficient for patients with Fontan circulation and cyanotic CHD and are contraindicated in earlier mentioned conditions (85). Besides indications, patient characteristics may make NOACs preferable over VKA. In patients with poor anticoagulation control on VKA, <66% were shown to have a greater reduction in bleeding events associated with NOACs (88). Cardiac failure was a risk factor for poor anticoagulation in Paper II and was also reported earlier (62). Additionally, NOACs have been associated with fewer intracranial hemorrhages in patients with cardiac failure (89), which may promote use of NOAC in these patients. Renal insufficiency (NOACs are dependent on the kidneys for elimination) has been shown to be prevalent in ACHD, with 50% of patients presenting with some degree of renal dysfunction (90). Renal insufficiency together with underweight patients may restrict the use of NOACs in ACHD. Liver disease interferes with drug

metabolism and patients with liver disease were excluded from important NOAC trials (91). Due to this, NOACs are recommended to be used with caution in patients with Child-Turcotte-Pugh B cirrhosis and class C cirrhosis (91).

Female gender was reported to be a risk factor for poor anticoagulation quality with VKA in Paper II and also earlier studies. Younger age was also a risk factor. NOAC may thus be a suitable alternative in young women. However, the contraindication for NOAC during pregnancy and breastfeeding limits this use (91). Lastly, drug interactions with NOACs must also be considered (91).

Limitations

Paper I was limited was limited by a small study population. Dates for the different examinations of echocardiography, stress test, NT-proBNP, NYHA class and cardiac MRI varied. Echocardiography may also have been performed by different cardiologists, enabling interobserver variability.

For all studies included in this dissertation, limitations are prone to those of the retrospective study design, such as missing data, important variables may be missing, unknown and unnoticed biases, recall bias, unrecognised confounders, absence of matched controls and differences in baseline characteristics compared to other studies.

For **Paper II** limitations concerned mainly a small population, the retrospective study design and consequently limited analysis of earlier reported predictors of anticoagulation quality. Methods of adjusting anticoagulation dosage may also have varied over time. It could also be reflected on, if INR-values during initiation of therapy should be included, as these may fluctuate. However, they constitute a small portion of the TTR. Factors such as psychiatric disorders, alcohol consumption, liver failure, vascular disease and history of bleeding are factors that may affect the anticoagulation quality, but could not be included due to a prevalence of <5%. This was also the case for Paper III. As some drugs are known to interact with VKA, these could be screened, adjusted for or excluded.

For **Papers II-IV**, systematic errors may be a limitation, as input to AuriculA and medical journals for diagnoses such as diabetes mellitus, medications or hypertension may differ or be set incorrectly.

For **Papers II-IV**, registers AuriculA and SWEDCON were an important source of data. Due to this, random errors are a possible limitation, as data input is prone to individual errors.

Paper III, although large for studies on ACHD, is limited in size and constitutes a heterogenous population. For investigating determinants of poor TTR and high INR variability, the medical journals we searched lacked reliable data on all earlier reported factors and could therefore not be analysed or included in the multivariate analysis, which is a strength of our study. Risk factors were calculated for TE and major bleeding together. For the multivariate analysis for these risk factors, the covariates adjusted for were similar, however, a separate analysis for each complication would be optimal.

Conclusions

Paper I

- The right ventricular GLS measured with echocardiography may be useful in the evaluation of systemic right ventricular function.

Papers II-IV

- Anticoagulation with VKA was of high quality in ACHD in the South of Sweden.
- A low incidence of TE and major bleeding events was seen in ACHD patients with high quality VKA therapy.
- Young age, female gender and cardiac failure may be cause for cautiousness and, where suitable, consideration of alternative non-VKA anticoagulants.
- History of TE was associated with complications (TE and major bleeding).
- One might consider implementing NOAC therapy in the absence of a highly specialised organisation in regard to VKA medication where close monitoring of the patient is not possible.
- TTR>65% is recommended for ACHD patients.
- NOAC appear safe and effective in ACHD patients without mechanical valve protheses, in line with earlier reported findings

Future perspectives

We have shown that the right ventricular GLS measured with echocardiography may be useful in the evaluation of systemic right ventricular function. However, the heart failure in in systemic RV is not fully understood yet and we need further studies to try to better prevent and treat the heart failure. There is still no proof that heart failure medications such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta blockers or aldosterone antagonists improve outcome in systemic RV failure.

We have shown that NOAC appear safe and effective in ACHD with the predominant indication atrial arrhythmia. However, our study is limited by small patient numbers. In the general population NOAC is recommended in atrial arrhythmias based on the CHA2DS2-VASc score. However, for ACHD patients especially in moderate and complex CHD with atrial arrhythmias a scoring system for indication of anticoagulation is still needed.

Prospective larger studies on use of NOAC in in ACHD would be of value to determine efficacy and safety.

Populärvetenskaplig artikel

Vuxna med medfödda hjärtfel är en ny och växande patientgrupp. Detta på grund av framsteg som gjorts inom behandling, både medicinsk och kirurgisk, för barn och för vuxna. Samtidigt finns en risk för komplikationer senare i livet. Vuxna med medfödda hjärtfel är en relativt ny och starkt växande patientgrupp som kräver särskilda kunskaper och avvägningar för omhändertagande och behandling vilket kan innebära en svårighet för sjukvården. Patientgruppen löper ökad risk för hjärtrytmrubbningar och en ökad risk på 10–100 gånger högre för blodpropp.

Huvudsyftet med avhandlingen var att dels undersöka om det finns alternativa metoder än hjärtmagnetröntgen för bedömning av kammarfunktionen hos patienter som har högerkammaren som systemisk, istället för vänsterkammaren. Systemisk innebär att det är denna kammare som pumpar ut syrerikt blod i kroppen.

Senare handlade den större delen av avhandlingen om att utvärdera hur bra den blodförtunnande behandlingen, med preparatet Waran, var hos vuxna med medfödda hjärtfel, om hur vanligt det var att få blodpropp eller drabbas av blödningar samt om det fanns särskilda egenskaper hos patienterna som ökade risken för nämnda komplikationer, som till exempel kön eller hjärtsvikt. Slutligen gjordes en studie på samma patientgrupp, men med den nya blodförtunnande behandlingen kallad NOAK (nya orala antikoagulantia (blodförtunnande)), där förekomsten av blodproppar och blödningar över tid undersöktes.

Det första arbetet visade att det fanns ett samband mellan ett mått på hjärtultraljud och hjärtmagnetröntgen som potentiellt kan möjliggöra att man kan använda detta mått vid värdering och uppföljning av hjärtfunktionen hos patienter med en systemisk högerkammare.

Det andra och tredje arbetet visade för första gången att kvaliteten av blodförtunnande behandling med Waran var av hög kvalitet hos vuxna med medfödda hjärtfel. Vi såg en låg förekomst av komplikationer som blodproppar och blödningar hos patienterna. Yngre ålder, kvinnligt kön och hjärtsvikt var egenskaper som ökade risken för låg kvalitet av blodförtunnande Waranbehandling. Vi såg att man kan ha samma behandlingsmål med Waran för vuxna med som utan medfödda hjärtfel. **Sista arbetet** visade att NOAK verkade vara en säker och effektiv behandling hos vuxna med medfödda hjärtfel utan hjärtklaffproteser.

Slutsatserna är att Waranbehandling av hög kvalitet är säkert och effektivt hos vuxna med medfödda hjärtfel. I framtiden behövs större studier för att utvärdera effekten och säkerheten för NOAC hos vuxna patienter med medfödda hjärtfel.

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About the author

Daniel Samarai studied medicine at Lund University and graduated 2018, followed by an internship at Lund Hospital. He is currently a resident in Family Medicine at a clinic in his hometown Malmö.

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