Diplomarbeit

Inzidenz von atrialen Hochfrequenzepisoden bei Schrittmacher- und ICD-PatientInnen

eingereicht von

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zur Erlangung des akademischen Grades

Doktor der gesamten Heilkunde

(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt an der

Universitätsklinik für Innere Medizin

Klinische Abteilung für Kardiologie

unter der Anleitung von

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Graz, 20.09.2021

Eidesstattliche Erklärung

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Graz, am 20.09.2021 Markus Feichtenhofer eh.

Preface

Dr. David Zweiker initially sparked my fascination for cardiology during the course echocardiography and exceptional bedside teaching in the Division of Cardiology of the University Hospital Graz in med school. A few weeks after this course, I decided to contact Dr. David Zweiker and asked him if I could somehow be a part of current research conducted by the Division of cardiology. He told me that I could help him conduct a study concerning particular arrhythmias. I gladly joined his project and helped to gather patients and data for the project.

A short time later, he inspired me to start my diploma thesis with Dr. Daniel Scherr and himself as supervisors using a part of the gathered data for this thesis.

Acknowledgements

First and foremost, I want to express my deepest gratitude to my supervisor Dr. scient. med. Dr. med. univ. David Zweiker, who always guided me during my diploma thesis. His extraordinary knowledge and passion for cardiology inspired me throughout the whole process.

Furthermore, I would like to extend my sincerest thankfulness to Univ. Prof. Priv.-Doz. Dr. med. univ. Daniel Scherr for giving me the opportunity to write my diploma thesis with him as supervisor.

Additionally, I want to express my gratitude for Univ.-Prof. Dr. Andreas Zirlik, Head of the Department of Cardiology at the University Hospital Graz, and his team for supporting me during the data collection for my clinical trial.

Finally, I´m thankful to my family, friends, and colleagues for their continuous support and never-ending patience during the completion of this diploma thesis.

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Glossary, Abbreviation and Acronyms

AF	Atrial fibrillation
AFL	Atrial flutter
AHRE	Atrial high-rate episodes
AV block	Atrioventricular block
BPEC	British Pacing and Electrophysiology Group
bpm	Beats per minute
CIED	Cardiac implantable electronic device
CMP	Cardiomyopathy
ECG	Electrocardiogram
ESC	European Society of Cardiology
i.v.	Intravenous
ICD	Implantable cardioverter defibrillator
ICM	Implantable cardiac monitor
IVCD	Intraventricular conduction disorders
ms	Milliseconds
NASPE	North American Society of Pacing and Electrophysiology
NYHA	New York Heart Association
PMC	Premature ventricular complexes
SND	Sinus node disease, sick sinus syndrome
SVT	Supraventricular Tachycardia
TIA	Transient ischaemic attack
VT	Ventricular Tachycardia

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Zusammenfassung

Einleitung:

Atriale Hochfrequenz Episoden (atrial high rate episodes, AHRE) stellen eine relativ neue Gruppe von Arrhythmien dar. Grundlage für die Detektion solcher Episoden stellen Neuerungen im Bereich der Schrittmacher und ICD-Technologie über die letzten Jahrzehnte dar. Das Auftreten dieser Episoden ist aus diesem Grund über die letzten Jahre Basis diverser klinischer Studien. Dennoch existieren derzeit noch nicht ausreichend Studien um das derzeitige Management und die Risikostratifikation optimieren, sowie eine genaue Aussage bezüglich tatsächlicher Epidemiologie, Progredienz und eventuellen Folgeerkrankungen (z.B.: Insult, TIA, systemische Embolie) tätigen zu können.

Methode:

Es handelt es sich um eine unizentrische Beobachtungsstudie mit einem Patientenkollektiv von 42 PatientInnen mit implantiertem kardialem elektronischem Gerät, welche an der Universitätsklinik für Innere Medizin Graz, Abteilung für Kardiologie von 2018 bis 2020 durchgeführt wurde. Im Rahmen der Einschlussvisite konnte eine Schrittmacher/ICD-Speicherauslese sowie der Anlage eines 24h-Holter-EKG durchgeführt wurden. Sechs Monate nach der Einschlussvisite erfolgte eine Kontrollvisite mit nochmaliger Speicherauslese des implantierten Schrittmachers/ICD und Anamnese. Anschließend wurden die erhaltenen Ergebnisse mittels SPSS Statistics Version 27.0 (IBM, Armonk, NY) aufbereitet und analysiert.

Ergebnisse:

Insgesamt konnten 42 Patienten mit implantierten kardialen elektronischen Geräten in die Studie eingeschlossen werden. Im weiteren Verlauf mussten 12 PatientInnen aufgrund der fehlenden Kontrollvisite nach 6 Monaten ausgeschlossen werden. AHRE konnten im Rahmen der Einschlussvisite bei 38,1% und im Laufe der Kontrollvisite in 26,7% der ProbandInnen nachgewiesen werden. Im Verlauf der Studie mussten zwei Patienten hospitalisiert werden, keiner dieser Hospitalisierungen ist auf eine kardiovaskuläre Ursache zurückzuführen.

Diskussion:

Diese Studie bestätigt, dass AHRE ein häufiges Phänomen bei PatientInnen mit implantierten kardialen elektronischen Geräten darstellt. Die klinische und therapeutische Signifikanz hingegen bleibt weiter unklar. Des Weiteren ist aus der statistischen Analyse ersichtlich, dass PatientInnen mit einem CHA_2DS_2VASc-Score über 4 ein höheres Risiko haben AHRE zu entwickeln. Zusätzlich konnte im Rahmen der Studie eine deutlich höhere Detektionsrate dieser Episoden durch Speicherauslese des implantierten Devices im Vergleich zu 24h-Holter-EKG-Analyse festgestellt werden.

Abstract

Introduction:

The term atrial high-rate episode (AHRE) describes a relatively new discovered arrhythmia. Improvements in CIED technology over the past few decades made the detection of these episodes possible. Therefore, these episodes became part of a variety of clinical trials. However, due to still limited evidence, further studies are required to optimize management, risk stratification and to obtain a better understanding concerning the epidemiology, progression to clinical atrial fibrillation and adverse events (e.g., stroke, TIA, systemic embolism).

Methods:

This trial is designed as a prospective monocentric observational study conducted at the University Hospital Graz / Department of Internal Medicine / Division of Cardiology. 42 CIED patients have been included from 2018 to 2020. The baseline assessment was paired with retrieving data from the implanted pacemaker or ICD memory unit and a 24h-Holter-ECG installation. A follow-up assessment was performed six months after the initial evaluation, including a data collection from the CIED and anamnesis. Statistical analyses of the gathered data were performed using SPSS Statistics Version 27.0 (IBM, Armonk, NY).

Results:

42 patients with CIED were included during the baseline assessment. Unfortunately, 12 of these patients had to be excluded from further analyses since these patients missed the follow-up assessment. The gathered data revealed a prevalence of atrial high-rate episodes in around 38,1% of CIED-patients during baseline assessment and in 26,7% of CIED-patients during their six-month follow-up evaluation. Two of the included patients needed a hospitalization during the six-month trial. None of the hospitalizations were due to an underlying cardiovascular cause. No patient suffered from a TIA, stroke, or other cardiovascular events.

Discussion:

This clinical trial confirms that AHRE is a common phenomenon in CIED-patients, while the clinical and therapeutic significance remains unknown. Furthermore, patients with high CHA_2DS_2VASc-Scores (> 4) have a significantly higher risk of developing atrial high-rate episodes. Additionally, 24h-Holter-ECG showed a significantly lower detection rate than CIED memory analyses regarding AHRE, suggesting implanted devices as the primary diagnostic tool.

1 Introduction

1.1 Cardiac Arrhythmias

1.1.1 Bradycardia

Bradycardia is defined as a heart rate below 60 beats per minute in adults other than athletes. There are multiple cardiac changes or abnormalities in the sinus node, atrial tissue, atrioventricular node tissue and the specialized conduction system that can lead to this condition. Extracardiac causes can also be causative for certain forms of bradycardia. (1)

1.1.1.1 Sinus Node Disease

Sick sinus syndrome (sinus node disease, SND), is defined as the sinus node's inability to create an appropriate heart rate for the body. It can lead to a whole range of cardiovascular adverse events like syncope, heart failure or atrial fibrillation. The pathophysiology consists of a complex electrophysiologic and structural remodelling, including different parts in this complex conduction and pacemaker system. (1-3)

The aetiology can be split into two groups. The first group contains intrinsic factors (e.g., fibrosis, ion channel dysfunction, remodelling), whilst the second one consists of extrinsic factors (e.g., metabolic disturbances, autonomic dysfunction, pharmacologic agents). (4)

Electrocardiogram, structured observation, and anamnesis of bradycardia-related symptoms are crucial for diagnosing a sinus node disease. Clinical presentation varies from mild fatigue or intermittent palpitations to syncope. ECG findings suggesting SND include sinus bradycardia, sinoatrial pause of more than 3 seconds, sinoatrial exit block, or sinus arrest. In some cases, atrial fibrillation occurs in combination with a sinus node disease. This combination can lead to a so-called Tachycardia-Bradycardia-Syndrome, where an episode of tachycardic atrial fibrillation or supraventricular tachycardia is followed by an asystolic pause, as shown in Figure 1. (5)

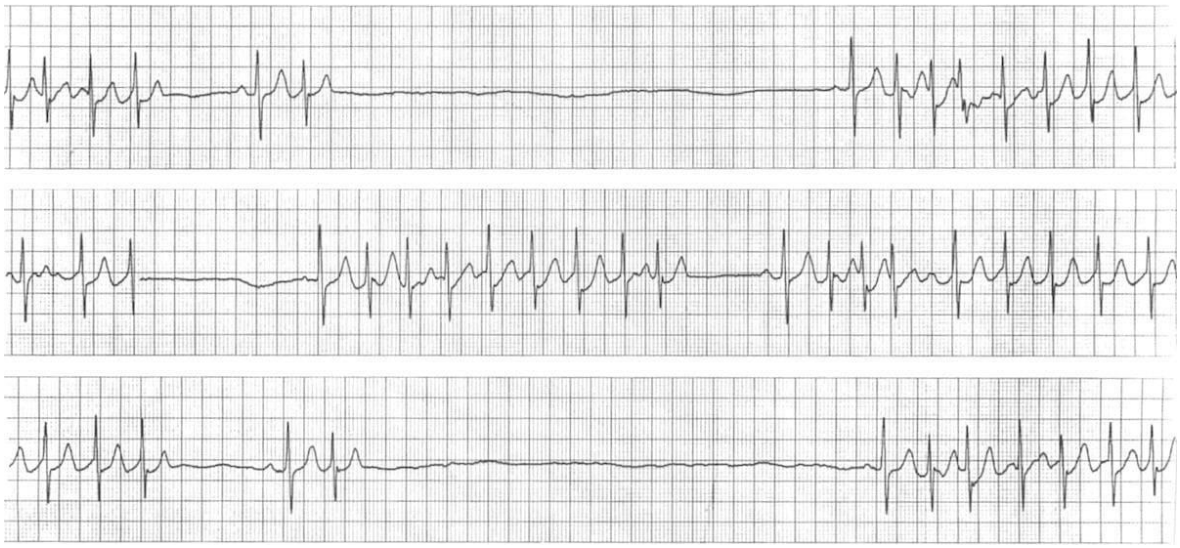

Figure 1 - Tachycardia-Bradycardia-Syndrome (ECG by litfl.com is licenced under CC BY-NC-SA 4.0)

In absence of bradycardia-related symptoms, no treatment is recommended. On the other hand, if SND causes the previously mentioned symptoms, a pacemaker implantation is indicated depending on the severity of symptoms and existing risk factors. (5)

1.1.1.2 Atrioventricular Block

Atrioventricular block (AV block) is defined as a condition where the conduction from atria to ventricles is impaired due to various reasons. Generally, these blocks are divided into three main categories by well-defined ECG-criteria. These three categories will be discussed in the following paragraphs. Symptoms, as well as the treatment, mainly depend on the degree of given AV block. The primary tool for evaluating and characterizing cardia arrhythmias (e.g., AV block) is an ECG. Other diagnostic tools include a structured anamnesis, physical examination, and in some cases, a 24h-Holter-ECG. A wide range of causes can be found, varying on the given degree. Certain medications (e. g. beta-blockers, adenosine, digitalis, amiodarone) could also lead to different degrees of AV blocks. (6)

1.1.1.2.1 First-Degree AV Block

A prolonged PR-Interval without interruption of AV conduction in an ECG characterizes a first-degree atrioventricular block. A time span of more than 200 ms between the beginning of the P-wave and the R-spike is the definition of a prolonged PR interval. Without interruption of the AV conduction means that each P-wave is followed by a QRS-complex. In some cases, a first-degree AV block could appear as a "masked" block. The reason for such a masked AV block is a PR interval greater than 300 ms, and due to this delay, the P-wave might be buried in the previous T-wave. (6, 7)

A common cause for a first-degree AV block is an increased vagal tone often found in athletes. Other causes include myocardial infarction, hyperkalaemia, myocarditis, or status post-cardiac surgery. Due to missing hemodynamic instability, the clinical presentation of a first-degree AV block is often asymptomatic. Therefore, no special treatment is indicated if the patient is asymptomatic. However, further clinical assessment for associated diseases and follow-up ECGs should be considered while AV block provoking medications such as adenosine, amiodarone, digitalis, beta-blockers should be switched or removed if possible. A pacemaker implantation should be considered in patients with a neuromuscular disease or if the conduction block is manifested within the distal conduction system. (1, 6, 7)

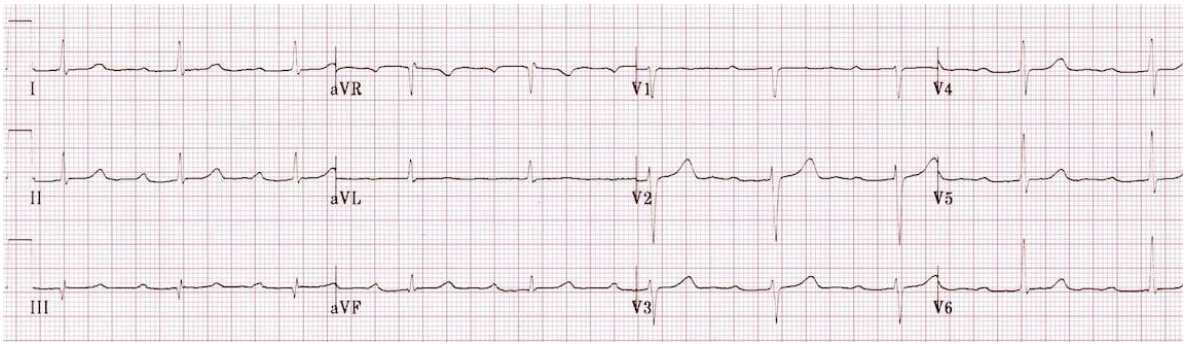

Figure 2 - First-degree AV block, PR interval > 200ms (ECG by litfl.com is licenced under CC BY-NC-SA 4.0)

1.1.1.2.2 Second-Degree AV Block

The second-degree AV block is described as an incomplete heart block and can further be divided into Type Mobitz I (Wenckebach) and Type Mobitz II by examining the PR interval. The atrioventricular conduction is intermittently blocked. This results in periodically occurring P-waves without following QRS-complexes. However, there is still a remaining connection between the atrium and the ventricle. The conduction failure often appears in regular patterns (e.g., 2:1, 3:1, 3:2). The differentiation between these two types is crucial for the correct management and treatment. In both types, an assessment for underlying diseases should be conducted. (6, 8, 9)

ECG findings suggesting an AV block Mobitz Type I/Wenckebach is a periodically extending PR interval followed by a failure of the conduction from atria to ventricle. This conduction failure results in a normal P-wave without following QRS-complexes. Like a first-degree AV block, Mobitz Type I is usually asymptomatic and, therefore, a benign rhythm. Still, due to reduced cardiac output, dizziness and syncope can be found in symptomatic patients. The risk of further progressing complete/third-degree AV block is low compared to Mobitz Type II. (6, 9)

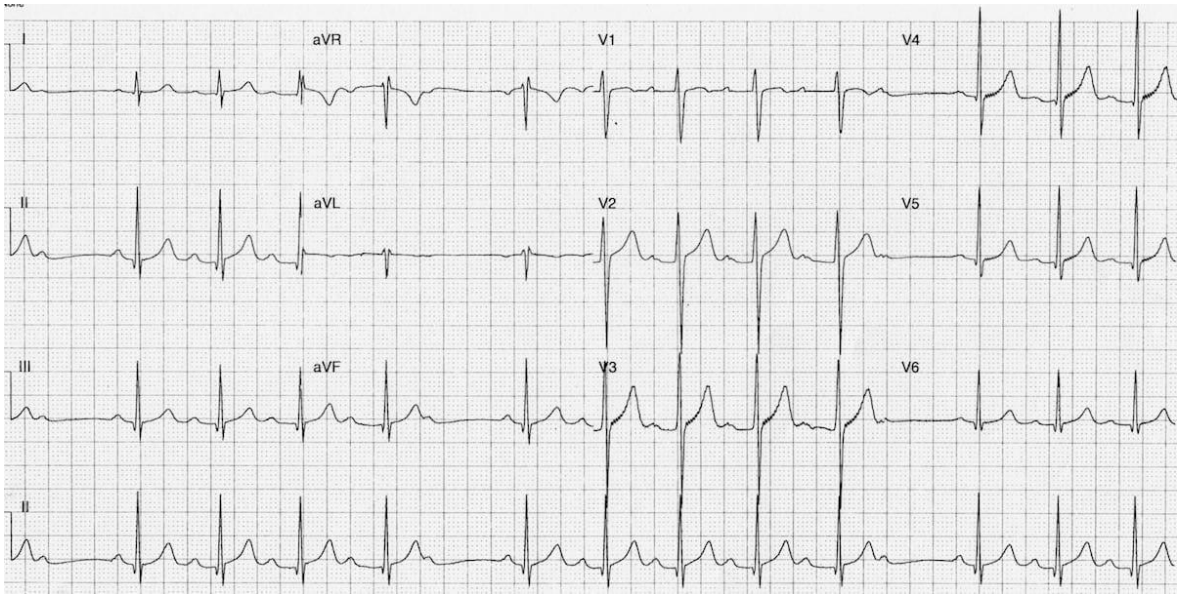

Figure 3 - Second-degree AV-block Type Mobitz I/ Wenckebach, P:QRS ratio 5:4 and 6:5 (ECG by litfl.com is licenced under CC BY-NC-SA 4.0)

Asymptomatic patients do not require a particular treatment, although follow-up monitoring and optimizing the current medication is indicated. In case of a hemodynamically unstable symptomatic patient, Atropine should be administered as acute therapy. Hemodynamically stable patients, on the other hand, should be monitored. If the symptoms are irreversible, or a neuromuscular disease, that is associated with the conduction system is diagnosed, a pacemaker implantation is recommended. (1, 6)

Mobitz Type II AV block is characterized by an intermittent atrioventricular conduction failure without a progressive prolongation of the PR interval. This missing prolonged PR interval is the main criteria to differentiate between Mobitz Type I and Type II. The impulse conduction failure occurs below the atrioventricular node further along the conduction system, including the His bundle, Tawara branches (left and right bundle branches), and the three fascicles (left anterior and posterior fascicles and right fascicle), mostly resulting in wide QRS-complexes. In a Mobitz type II block, the ventricular rate is usually a fraction of the atrial rate, leading to particular conduction patterns (e. g. 2:1, 3:1, 3:2). Another typical finding is a pre-existing LBBB (left branch bundle block) or bifascicular block that in combination with an intermittent block of the remaining fascicle leads to this second-degree AV block. (6, 8, 9)

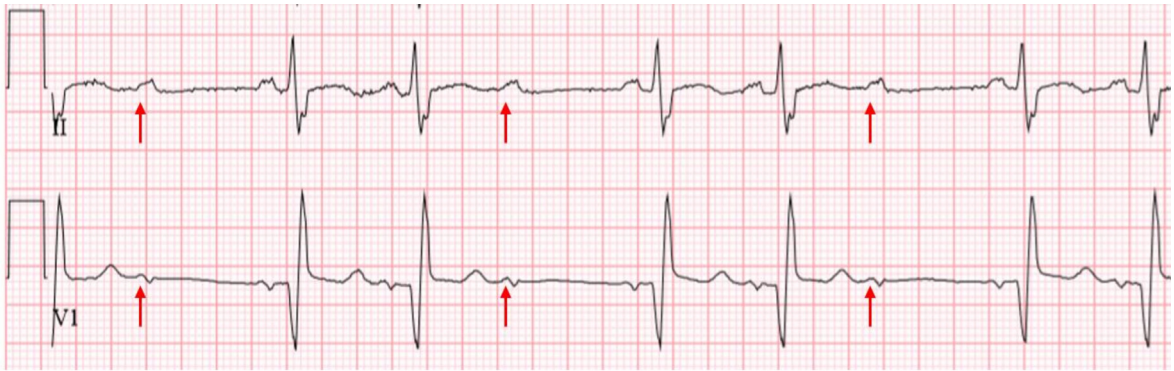

Figure 4 - second-degree AV block type Mobitz II, Î non-conducted impulse (ECG by litfl.com is licenced under CC BY-NC-SA 4.0)

This condition is often the result of structural damage to the cardiac conduction system due to fibrosis, necrosis, or myocardial infarction. Mobitz Type I is typically consequential to a functional problem. Infections (e.g., myocarditis, Lyme disease, rheumatic fever), infiltrative (e.g., amyloidosis, sarcoidosis, hemochromatosis), and autoimmune diseases (e.g., SLE, systemic sclerosis) are other known causes for an atrioventricular block Mobitz type II. (6, 8, 9)

Typical clinical findings include fatigue, chest pain, dizziness, dyspnoea, and syncope resulting from existing bradycardia. Also, the risk of further progressing into a complete heart block is, compared to first-degree AV block and Mobitz type I block, high. Therefore, a Mobitz Type II block is a life-threatening condition and requires close monitoring and treatment. In hemodynamically stable patients, this treatment consists of monitoring, further assessment of underlying diseases and reversible causes as well as a pacemaker implantation if the condition is irreversible. The initial administration of atropine should be considered in hemodynamically unstable patients. However, unlike Mobitz type I, the patient's condition could even worsen due to atropine if the block is located below the bundle of His. If no improvement is seen, temporary cardiac pacing might be required as part of the acute management. (1, 6)

1.1.1.2.3 Third-Degree AV Block

The last category is referred to as complete heart block or third-degree AV block. In patients with this condition, the atrioventricular conduction is completely blocked; therefore, the heart rate depends on a given ventricular escape rhythm or junctional rhythm. If no escape rhythm can be established, the patient may suffer from a ventricular pause leading to syncope and further on to sudden cardiac death. The ECG finding in patients with third-degree AV block is a complete AV dissociation, which means P-waves and QRS-complexes bear no relation to each other. (6, 10)

If the block occurs above the bundle of His, the AV node will generate an intrinsic heart rate of about 40 - 50 bpm and narrow QRS-complexes. This complete AV block could also appear below the bundle of His, leading to wide and deformed QRS-complexes with a heart rate of approximately 20 - 40 bpm, produced by a ventricular pacemaker. The prognosis also depends on the location inside the conduction system, meaning a distal block leads to a worse prognosis, while a proximal location results in a better outcome. Clinical findings in patients with complete heart block vary from nausea and dizziness to potentially life-threatening conditions like an Adam-Stokes attack or sudden cardiac arrest. The severity mainly depends on the ventricular escape mechanism and resulting heart rate. If no reversible cause can be found, the long-term treatment for this patient group is a pacemaker implantation. Acute management includes cardiac monitoring, further clinical assessment, temporary cardiac pacing (transvenous or transcutaneous) and atropine. Like in AV block Mobitz II, atropine could worsen the patient's condition if the block is located below the bundle of His. In this case, the administration of catecholamines should be considered. (6)

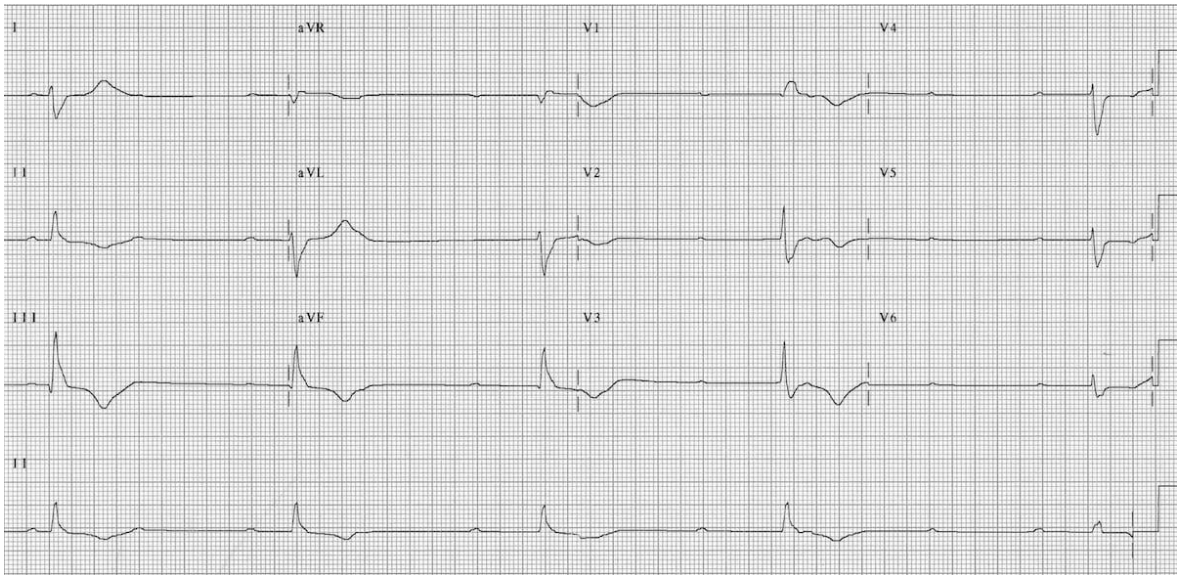

Figure 5 - third-degree AV block, atrial rate 60 bpm, ventricular rate 30 bpm, wide QRS (ECG by litfl.com is licenced under CC BY-NC-SA 4.0)

1.1.1.3 Intraventricular Conduction Disorders

Intraventricular conduction disorders (IVCD) can be divided into unifascicular, bifascicular and trifascicular blocks due to the anatomical structure of the conduction system. (11) Each type is associated with specific clinical significance and findings. Thus, leading to different assessments and, if necessary, treatment. These intraventricular conduction disorders are relatively common ECG findings and can be found in asymptomatic patients as well as patients with underlying diseases. A main ECG-criteria for diagnosing intraventricular blocks is a widened QRS-complex (>100 ms). Therefore, more than 100 ms, suggest an incomplete block and more than 120 ms indicate a complete block. Additional findings are specific for the affected fascicle, meaning left anterior, left posterior or right fascicle. (12) Other common causes for a wide QRS-complex, besides a fascicular block, are nonspecific intraventricular conduction delay, left ventricular hypertrophy, ventricular pacing (right ventricle), ventricular tachycardia, pre-excitation syndrome, hypothermia, medical agents, or hyperkalaemia. (11) Regarding the underlying diseases, a further clinical assessment, including exercise ECG, 24h-Holter-ECG, echocardiography or in rare cases coronary angiography and electrophysiologic study, is recommended. (1, 11)

1.1.2 Tachycardia

Tachycardia is a term used for a heart rate > 100 bpm in adults (age-adjusted limits in children). Depending on the origin of the excitation, tachycardia is generally divided into supraventricular tachycardia and ventricular tachycardia.

1.1.2.1 Supraventricular Tachycardia

Supraventricular tachycardia (SVT) is an umbrella term for different forms of tachycardias that rise above the bifurcation of the bundle of His or depend on mechanisms involving the His bundle. The heart rate is usually above 100 beats per minute, although in some cases, the ventricular rate could differ from the actual supraventricular rate due to an AV block (13). SVT includes inappropriate sinus tachycardia, atrial tachycardia (focal and multifocal), AVRT, AVNRT, junctional tachycardia, atrial flutter, and atrial fibrillation. Atrial fibrillation is also part of this group and will be discussed separately in chapter 1.1.3. Paroxysmal is a commonly used term to further describe arrhythmias regarding abrupt onset and termination of an arrhythmic episode (14). The prevalence in the general population is 2,25 per 1000 persons, while women when compared to men are at twice the risk and persons older than 65 years are at a fivefold increased risk compared to younger individuals. (15)

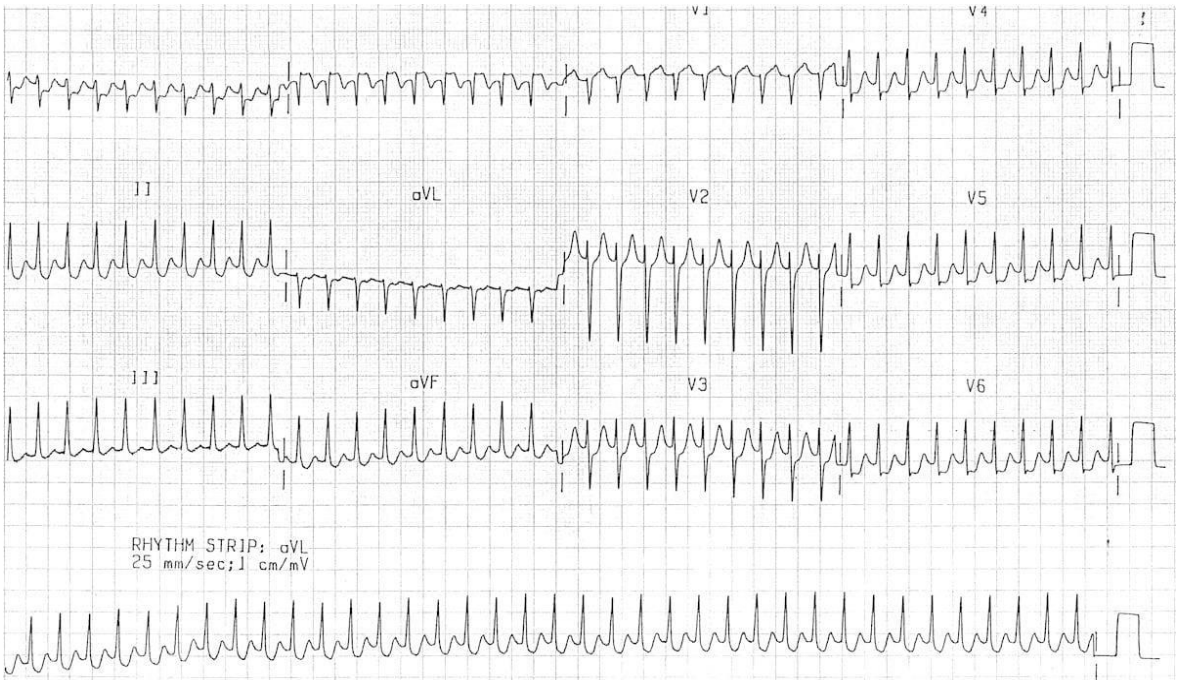

Figure 6 - orthodromic atrioventricular re-entry tachycardia (ECG by litfl.com is licenced under CC BY-NC-SA 4.0)

Clinical presentation of patients suffering from SVT is manifold due to various factors (e.g., age, constitution, comorbidities). The wide range of symptoms stretches from palpitations, dyspnoea, fatigue, chest pain, and loss of consciousness. In addition, the severity of these symptoms might differ significantly. (13, 15)

A structured anamnesis paired with a physical examination should initially be performed to evaluate a patient presenting with tachycardia-related symptoms. The main tool for diagnosing SVT is a 12-lead ECG. A common finding in the case of an SVT is a QRS-complex shorter than 120 ms. However, wide QRS-complexes (> 120 ms) might be present in a coexisting bundle branch block or antegrade conduction over accessory pathways. Therefore, wide QRS-complexes typically suggest a ventricular tachycardia and should be treated as VT until proven otherwise. Further assessment includes blood samples, echocardiographic imaging, 24h-ECG, and in special cases vagal manoeuvre, adenosine administration, or electrophysiological study. (15)

The acute treatment for patients suffering from narrow (<120 ms) QRS-complex tachycardia depends on their hemodynamic stability. Electrical cardioversion is indicated as first-line therapy in unstable patients. Hemodynamic stable SVTs, on the other hand, should be managed with an initial vagal manoeuvre and, if not terminated, i.v. adenosine administration or as third step other i.v. medications (e.g., beta-blocker, verapamil or diltiazem). Long-term treatment, on the other hand, depends on the specific underlying mechanism of given supraventricular tachycardia. (15)

1.1.2.2 Ventricular Arrhythmia

The term ventricular arrhythmia sums up the following arrhythmias (16, 17):

- Premature ventricular complexes
- Ventricular tachycardia
- Torsades de pointes
- Ventricular flutter
- Ventricular fibrillation

Underlying pathophysiological mechanisms resulting in ventricular arrhythmia involve abnormal automaticity, triggered activity provoked by early or late afterdepolarizations, re-entry, and enhanced normal automaticity (17-19). Clinical presentation consists of a broad spectrum from palpitations, fatigue, dyspnoea, chest pain, syncope, loss of consciousness to hemodynamic instability and sudden cardiac death. Therefore, a fast and structured evaluation is needed. This evaluation initially consists of anamnesis and physical examination. Further evaluation should be performed using 12-lead ECG, blood samples, non-invasive cardiac imaging, such as echocardiography, CT or MRT. Invasive testing through heart catheterization or CT angiography is also recommended depending on given facts. (17)

Acute management contains electric cardioversion or ACLS (advanced cardiovascular life support) in hemodynamic unstable patients. In hemodynamic stable patients, on the other hand, cardioversion, verapamil, beta-blockers, procainamide are the recommended treatment strategies according to current guidelines.(17) Options for long-term treatment and prevention of VA consist of various Medications (e.g., Beta-blockers, Amiodarone, Sotalol, Verapamil), Defibrillators (e.g., ICD, wearable cardioverter-defibrillator, external defibrillator), and Catheter ablation. (17)

1.1.2.2.1 Premature ventricular complexes

Premature ventricular complexes (= ventricular extrasystoles) or PVC describes QRS-complexes originating below the bundle of His from an ectopic focus inside de ventricles. PVC may occur in particular patterns, forming bigeminy, trigeminy, quadrigeminy, couplet. The occurrence of ≥3 PVC in a row is named nonsustained VT, as described below (17). PVC is a common phenomenon documented in about 50% of all people (with or without heart disease) during long-term monitoring (20).

1.1.2.2.2 Ventricular tachycardia

Ventricular tachycardia or VT is defined as a cardiac arrhythmia of three or more consecutive QRS-complexes originating in the ventricles, resulting in a heart rate above 100 beats per minute (17).

Depending on the clinical and ECG presentation, different types are known (17):

- **Sustained:** VT subsisting for ≥ 30 s or requiring termination in < 30 s due to hemodynamic instability
- **Nonsustained:** spontaneously terminated VT without intervention
- **Monomorphic:** VT with stable, recurring QRS-complex morphology
- **Polymorphic:** VT with multiform or changing QRS-complex morphology

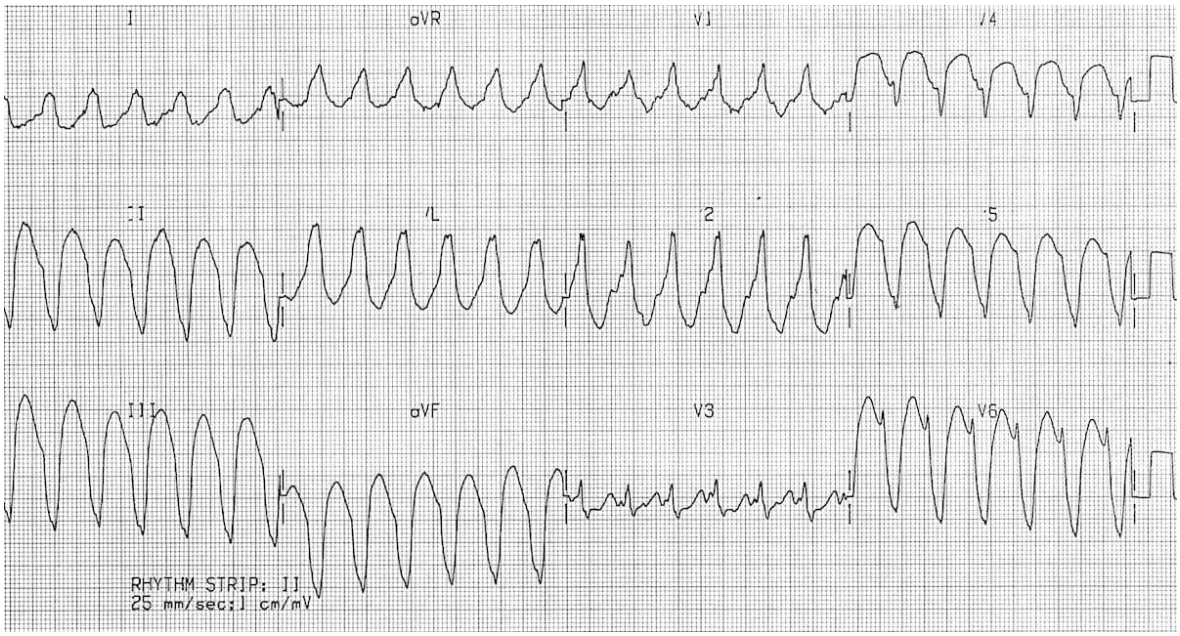

Figure 7 - Monomorphic VT (ECG by litfl.com is licenced under CC BY-NC-SA 4.0)

1.1.3 Atrial Fibrillation

Atrial fibrillation (AF) is the most common supraventricular arrhythmia worldwide. In the case of AF both atria contract ineffectively and irregularly, following an uncoordinated electrical activation. Primary tool for diagnosing this condition is the electrocardiogram. Without correct management, this disease could lead to a series of secondary events (e.g., stroke, CMP, acute left ventricular failure). Therefore, making the correct diagnosis as well as the right treatment is essential in preventing further harm. (21)

1.1.3.1.1 Epidemiology

In 2010 Sunmeet S. et al. conducted a systematic review in which this group of scientists compared 184 studies concerning the epidemiology of AF. (22) They found an incidence of 77,5 (men) per 100 000 person-years and 59,5 (women) in 2010 compared to 60,7 (men) and 43,8 (women) in 1990. The global prevalence rates per 100 000 people increased from 569,5 to 596,2 in men and 359,9 to 373,1 in women over the same time. This prevalence highly increases with advancing age. Thus, only 1% of patients with AF are younger than 60 years of age, while one third of the patients is older than 80 years. (23) Age-adjusted mortality rates in both men and women showed a two-fold increase over this time (men 0,8 per 100 000 to 1,7 and women 0,9 to 1,9). Therefore, these results show a significantly increasing incidence, prevalence, and mortality over the time span of 20 years (1990 to 2010). However, the epidemiology strongly varies in different countries worldwide. (22)

1.1.3.1.2 Pathophysiology

The underlying mechanisms that lead to AF are yet not fully understood. However, multiple structural and electrophysiological abnormalities triggering or maintaining AF are already identified. (24) Structural abnormalities increasing the risk of AF include different diseases that lead to architectural changes in the atrial tissue (e.g., CAD, CMP, increased LA pressure, hypertension, valvular heart disease). (25-27) In some cases infiltrative diseases like sarcoidosis, hemo-chromatosis or amyloidosis could also promote AF. Further extracardiac risk factors consist of obesity, hyperthyroidism, sleep apnoea, use of alcohol or drugs. (26)

Electrophysiological mechanisms, on the other hand, can both trigger and maintain AF. The most common electrophysiologic trigger is, amongst others, an ectopic focal pacemaker located in the region around the left atria's pulmonary veins. (28) Therefore, this discovery led to different catheter ablation strategies concerning the pulmonary veins. (24) The coronary sinus, venae cavae, atrial appendages, septum and ligament of Marshall are other less common locations for ectopic foci triggering AF.

Various theories concerning the maintenance of AF are still being discussed (e.g., reentry circuit, rapidly firing foci, multiple wavelets). (29, 30) Another provoking factor is the autonomic stimulation by both sympathetic and parasympathetic branches. (31)

In a part of the patients, AF seems to occur without an underlying disease or risk factors. This condition is historically referred to as primary atrial fibrillation or lone atrial fibrillation. However, increasing knowledge and discoveries in pathophysiology suggest underlying causes and risk factors in almost every patient with AF. (21, 32)

1.1.3.1.3 ESC Classification (21)

- **Paroxysmal:** AF that persists for more than 48h and terminates spontaneously or due to iatrogenic intervention within seven days of onset
- **Persistent:** AF with a duration of more than seven days, but a termination (iatrogenic or spontaneous) and conversion into sinus rhythm is still possible
- **Long-standing persistent:** This is a term for continuous AF over more than 12 months
- **Permanent:** In this case a conversion into sinus rhythm is not possible or the primary intention. Therefore, no further attempts to terminate the AF will be undertaken.

1.1.3.1.4 Clinical Presentation

One-third of patients suffering from AF display an asymptomatic clinical presentation. Symptomatic patients might present with a variety of unspecific symptoms (e.g., palpitations, fatigue, syncope, chest pain, dizziness, anxiety, heart failure, stroke). (21, 33) Due to this wide range of symptoms, the European Heart Rhythm Association established a scoring system to further categorize the present AF-related symptoms and their impact on daily life. Palpitations, fatigue, dizziness, dyspnoea, chest pain and anxiety represent the evaluated symptoms for the modified EHRA-Score. (34)

Score	Symptoms	Description
1	None	No AF-related symptoms present
2a	Mild	AF-related symptoms present, no effect on normal daily activity
2b	Moderate	AF-related symptoms present, no effect on normal daily activity, patient troubled by symptoms
3	Severe	AF-related symptoms present, normal daily activity affected
4	Disabling	Normal daily activity not possible

Table 1 - mEHRA-Score (34)

1.1.3.1.5 4S-AF Characterization

In 2021 Potpara et. al. (35) issued a new approach to characterize AF and therefore improve treatment decisions. This scheme combines multiple aspects concerning AF, such as stroke risk, symptoms, AF burden, and substrate. Table 2 gives a brief overview of this so called "4S AF scheme". (35)

	Stroke risk	Symptoms	Severity of AF burden	Substrate
Description	Low risk of stroke?	Asymptomatic Moderate Severe	Spontaneously terminating? AF duration Density of episodes	Cardiovascular risk factors Comorbidities Atrial CMP
Assessment tools	CHA_2DS_2VASc-Score (21, 36)	mEHRA-Score (34) Quality of life Questions	ESC classification (21) Total AF burden	Clinical Assessment Imaging

Table 2 - 4S AF Scheme (35)

In this scheme, treatment aims concerning rate control and rhythm control depend on a scoring system including symptoms, AF burden as well as substrate, while the decision of whether a patient should undergo anticoagulation therapy or not solely depends on the risk of stroke (CHA_2DS_2VASc-Score) (35).

1.1.3.1.6 Assessment and Screening

The diagnostic assessment for atrial fibrillation includes 12-lead ECG, echocardiography (transthoracic), blood analysis (e.g., blood count, electrolytes, thyroid and kidney function) and evaluation of medical history. AF-related symptoms, concomitant conditions and AF pattern should be part of this initial evaluation. It is also strongly recommended to determine the CHA_2DS_2VASc-Score (Table 2) during this first assessment for further decisions in terms of treatment. Selected patient groups should be admitted to special diagnostic procedures (e.g., ambulatory ECG, transesophageal echocardiography, Brain-MRT) for further assessment. However, structured follow-up is suggested in every patient with diagnosed atrial fibrillation to optimize management and compliance. (16, 21)

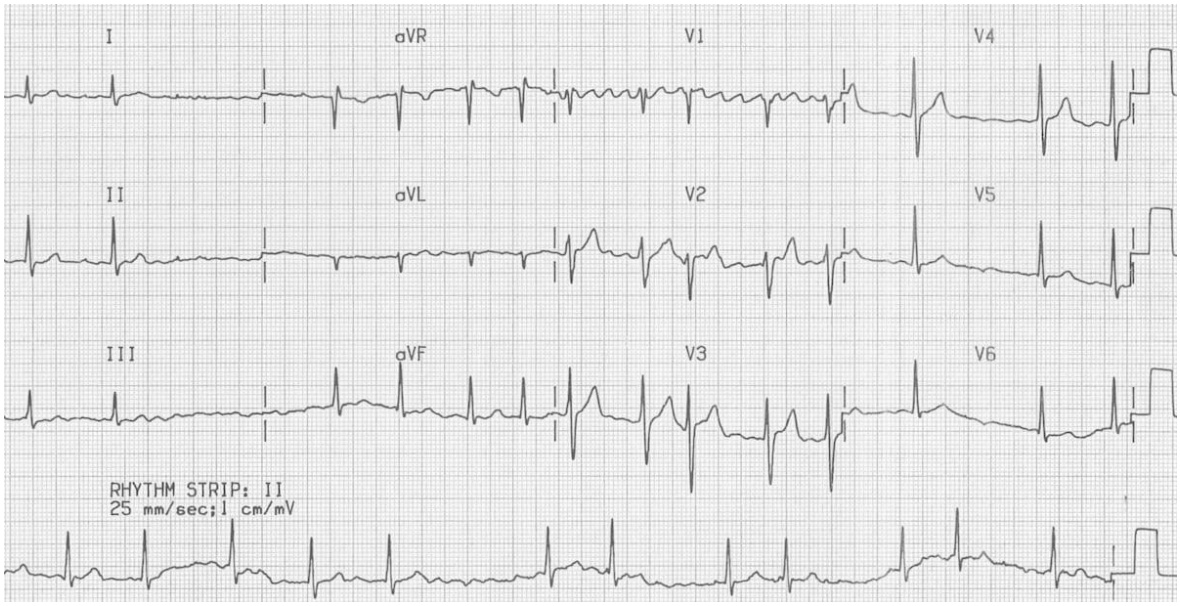

Figure 8 - Atrial Fibrillation (ECG by liftl.com is licenced under CC BY-NC-SA 4.0)

Common ECG-findings in patients with atrial fibrillation (12-lead-ECG) (16):

- Irregular RR-Interval
- Variable ventricular rate (bradycardia, normocardia, tachycardia)
- Absence of P-waves
- Fibrillatory waves (300 to 600 per minute)
    - Often prominent in recent-onset atrial fibrillation
- No isoelectric baseline
- Usually small QRS-complexes (> 120 ms)
- Indiscernible PR-Intervals

The ESC also issued recommendations for screening to detect atrial fibrillation. The first recommendation suggested by the ESC-Guideline 2020 refers to opportunistic screening in patients above 65 years of age due to increased prevalence in older patients (21). Currently, a wide range of different screening tools exists, including smartphone applications (e.g., intermittent ECG, photoplethysmogram), smartwatches, oscillometric blood pressure cuff, Holter-ECG, ECG-patches, ICM and simple palpation. Another recommendation by the ESC concerns pacemaker and ICD-patients. These patients should be screened for AHRE/subclinical atrial fibrillation during regular follow-ups. (21)

1.1.3.1.7 Treatment

The management for patients suffering from atrial fibrillation should be based on a patient-individualized pathway and carried out by not just one physician but also an interdisciplinary team, including specialists like cardiologists, pharmacists, and general practitioners. Treatment strategies might change over time due to development of new symptoms, risk factors and disease progression. A crucial part of this management is the patient's education, as it could significantly increase compliance of the patient and therapy adherence. Therefore, physicians should carry it out at an early stage of the disease. The ESC published the so-called ABC-pathway (`A` = anticoagulation/avoid stroke, `B` = better symptom management, `C` = cardiovascular/comorbidity optimization) as treatment approach in the „ESC Guidelines for the diagnosis and management of atrial fibrillation". (21)

1.1.3.1.7.1 `A` = anticoagulation/avoid stroke

The first part of this section is the evaluation of certain risk factors which increase the risk of stroke (e.g. diabetes mellitus, hypertension, age) to set the correct indication for possible anticoagulation. Common risk factors have been summarized in a scoring system, referred to as CHA_2DS_2VASc-Score (36, 37). A CHA_2DS_2VASc-Score of 0 in males or 1 in females suggests a low risk of ischaemic stroke and low mortality rates. In contrast, sums above 1 (male) and 2 (female) indicate a significantly higher stroke risk and therefore, appropriate treatment. (21, 36, 37)

Letter	Points	Description
C	1	Congestive heart failure
H	1	Hypertension or antihypertensive treatment
A	2	Age over 75 years
D	1	Diabetes mellitus
S	2	Stroke (e.g., previous stoke, transient ischaemic attack, thromboembolism)
V	1	Vascular disease (e.g., myocardial infarction, peripheral artery disease, coronary artery disease)
A	1	Age between 65 – 74 years
Sc	1	Sex category: female
Max.	9	(Age counts for 2 Points max)

Table 3 - CHA_2DS_2VASc-Score (21, 36)

Furthermore, the bleeding risk should also be considered. The most important clinical risk factors have been summarized in another scoring system, the so-called HAS-BLED-Score (37, 38). Rates from 0 to 2 predict a low bleeding risk, while a rate above 2 suggests an increased bleeding risk. A high bleeding risk should not lead to withholding oral anticoagulation but modifying the existing risk factors and frequently reevaluating them. (21)

A few absolute contraindications for oral anticoagulation exist, including severe active bleeding, recent high-risk-bleeding, and associated comorbidities (e.g. thrombocytopenia < 50000 platlets/µl). (21)

Letter	Points	Description
H	1	Uncontrolled Hypertension (systolic BP over 160 mmHg)
A	1-2	Abnormal renal and/or hepatic function (one point each), e.g. dialysis, transplant, serum creatinine > 200µmol/L, cirrhosis, elevated bilirubin, elevated ALT/AST
S	1	Stroke (previous ischaemic or haemorrhagic)
B	1	Bleeding predisposition or history (previus major haemorrhage, anaeimia or severe thrombocytopenia)
L	1	Labile INR (TTR less than 60%, only if patient is receiving VKA)
E	1	Elderly (age over 65 years or extreme frailty)
D	1-2	Drugs or excessive alcohol drinking (one point each)
Max.	9	

Table 4 - HAS-BLED-Score (21, 38)

After careful consideration of both scores appropriate treatment should be administered if indicated. Possible therapy strategies include vitamin K antagonists (=OAC), non-vitamin K antagonist oral anticoagulants (=NOAC) or left atrial appendage occlusion. The final decision concerning the specific substance should be made individually depending on various risk factors. (21)

1.1.3.1.7.2 `B` = better symptom management

The “better symptom management” approach consists of two groups, rhythm control and rate control. Rate control is often crucial to improve AF-related symptoms. First-line therapy to achieve a sufficient rate control indicates the use of medications (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, dioxin, amiodarone) (39). If rate control through medication fails, the attending physician should consider other ways to achieve rate control including ablation or pacing. (21, 40)

Rhythm control on the other hand, refers to the main goal of restoring and maintaining sinus rhythm. Various treatment approaches should be considered, including cardioversion, antiarrhythmic drugs (e.g., Amiodarone, Flecainide, Propafenone) or catheter ablation. The main indication for rhythm control is a reduction of AF-related symptoms as well as an improvement in Quality of life. (21, 40)

1.1.3.1.7.3 `C` = cardiovascular/comorbidity optimization

The third part of the ABC-pathway includes identifying and managing risk factors, diseases, and lifestyle factors that could lead to atrial remodelling or cardiomyopathy and, therefore, atrial fibrillation. Appropriate management of these factors leads to a reduction of symptom severity and AF burden. Lifestyle changes form the first group of interventions and consist of weight loss in obesity, reduction in alcohol consumption and physical activity. Hypertension, heart failure, coronary artery disease, diabetes mellitus and sleep apnoea should be managed according to current guidelines to reduce the risk of AF-development further. (21, 41)

1.2 Cardiac Implantable Electronic Devices

A wide range of cardiac implantable electronic devices (CIED) has been developed over the last decades to record, monitor, or even control the patients' heartbeat. Those devices include pacemaker, loop recorder, implantable cardioverter defibrillator, and biventricular devices. Due to this wide range of different devices, they find use in various diseases/disorders, of which the most significant ones are listed in the following chapters, as well as an overview of the features of currently used devices. (33, 42)

1.2.1 Pacemaker

Pacemakers find use in all kinds of arrhythmias (Chapter 1.2.1.3). Their main purpose is to reduce arrhythmia-related symptoms and provide an appropriate heart rate. These cardiac implantable devices consist of two primary parts. The first one is the pulse generator which contains a small processor and a battery along with an electrical circuit. This pulse generator is connected through an isolated lead (or leads) to an electrode (or electrodes) placed inside the atrium or ventricle of the patient's heart, which forms the second essential part (42). Over the past few years, new technologies led to the relatively new invention of leadless pacemakers, devices inserted directly inside the patient's ventricle. These devices combine the pulse generator and the electrodes in one location (43, 44). Varying on the given indication for the implanted device, single or multiple leads and electrodes can be inserted. The implantation of such devices is usually performed under local anaesthesia combined with intravenous sedation by an experienced doctor after careful consideration of the given indication. (45-49)

1.2.1.1 Modes of Operation

Currently used modes of operation in pacemakers are based on the revised NASPE/BPEG generic code for anti-bradycardia, adaptive-rate and multisite pacing pacing (50). This code consists of five positions, as listed in Table 1. Position 1 describes in which heart chamber (Atrium or Ventricle) pacing is possible, while position 2 shows potential locations for detecting cardiac depolarizations. Programmable options depend on the given implanted electrodes (e.g., Atrium, Ventricle, Both). The third letter represents whether a sensed signal inhibits or triggers a response by the implanted pacemaker.

The fourth position describes the presence of rate modulation (adaption). Finally, multisite pacing, represented by the fifth letter, indicates whether pacing in multiple sides in one chamber or pacing in multiple chambers (e.g., both atria, both ventricles) is possible. The programming of these modes strongly depends on the given indication, the condition of the patient's conduction system (e.g., AV block III°), and the implanted device. Therefore, it should be chosen individually by the attending clinician. (45, 49-51)

Position 1	Position 2	Position 3	Position 4	Position 5
Location Paced	Location Sensed	Response Mode	Rate Modulation	Multisite Pacing
A = Atrium	A = Atrium	T = Triggered	R = Rate Modulation	A = Atrium
V = Ventricle	V = Ventricle	I = Inhibited		V = Ventricle
D = Dual	D = Dual	D = Dual	0 = None	D = Dual
0 = None	0 = None	0 = None		0 = None
S = Single	S = Single			

Table 5 - NASPE/BPEC generic Pacemaker Code (50, 51)

1.2.1.2 Pacemaker Types (48)

- **Single Chamber Devices:** One electrode, placed inside the atrium or the ventricle
- **Dual Chamber Devices:** Two electrodes, one inside the atrium and one inside the ventricle
- **Biventricular devices:** at least two electrodes, one in each ventricle

1.2.1.3 Common Indications for Cardiac Pacing

The following list summarizes the currently most common indications for permanent pacemaker implantation according to the 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy (49). The actual implantation depends not only on these indications but also on arrhythmia-related symptoms, lifestyle limitations, existing risk factors and should be decided individually (46, 49, 52).

- Sinus Node Dysfunction (Sick Sinus Syndrome, SND)
- Atrioventriculer Block (advanced II° and III°)
- Bisfascicular block (Block below the AV node)
- Post myocardial infarction
- Recurring syncope caused by carotid sinus syndrome
- Neuromuscular diseases (e.g., myotonic dystrophy)
- Prevention of atrial arrythmias (e.g., recurrent, therapy resistant SVT)
- Long-QT Syndrome (e.g., pause dependent ventricular tachycardia)
- Cardiac resynchronization therapy
- Obstructive hypertrophic cardiomyopathy (e.g., aquired AV block, SND)
- Children with congenital heart disease (e.g., AV block, SND, postoperative)

1.2.2 Implantable Cardioverter-Defibrillator

Implantable cardioverter-defibrillators (ICD), similar to pacemakers, consist of a pulse generator and electrodes for pacing or sensing. In addition to these parts, a defibrillation coil is included in ICD-systems. Also, both ICD and pacemaker share the ability to monitor and store the patient's ECG. Anti-tachycardic pacing, cardioversion, and defibrillation, on the other hand, are unique functions used in ICDs. (53) Thus, these cardiac implantable electric devices find usage in various diseases/disorders for primary and secondary prevention of sudden cardiac death (45, 54).

1.2.2.1 Types

- **Transvenous devices (TV-ICD):** currently the most common implanted ICD-systems, the pulse generator is embedded subcutaneously in the pectoral region, while the electrodes are implanted transvenous. (53)
- **Subcutaneous devices (S-ICD):** Indicated in special groups (e.g., young patients, high risk of bacterial infections), implanted subcutaneous into the chest wall with a single subcutaneous lead and defibrillation coil; Pacing is not possible. (55)
- **Wearable devices (WCD):** temporary (bridging) therapy (high risk of SCD), no implantation needed, pacing is not possible. (56)

1.2.2.2 Modes of Operation

Similar to the coding system for pacemaker systems, the NASPE/BPEG also published a defibrillator code in 1993. This code consists of four digits. The first position describes the chamber in which the ICD-System should deliver the shock. The location of anti-tachycardia pacing is defined in the second letter, while the fourth letter codes the anti-bradycardia pacing side. The detection of tachycardia can be realized by electrogram alone (E) or in combination with hemodynamic (H) parameters (e.g., blood pressure, transthoracic impedance). This feature is coded in the third position of the NBD code. (57)

Position 1	Position 2	Position 3	Position 4
Shock Chamber	Pacing Chamber (anti-tachycardic)	Tachycardia detection	Pacing Chamber (anti-bradycardic)
A = Atrium	A = Atrium	E = Electrogram	A = Atrium
V = Ventricle	V = Ventricle		V = Ventricle
D = Dual	D = Dual	H = Hemodynamic	D = Dual
0 = None	0 = None		0 = None

Table 6 - NASPE/BPEG Defibrillator Code (57)

1.2.2.3 Common Indications for ICD Implantation

ICD-Implantation is recommended in two main groups of indications according to the ACC/AHA/HRS Guidelines for device-based Therapy 2008 (45). Secondary prevention of sudden cardiac death summarizes the first group of indications, individuals in this group already suffered from at least one sudden cardiac arrest. The second group sums the primary prevention of sudden cardiac death in patients without a prior cardiac arrest. A detailed list of the most relevant indications according to the current guidelines is stated below. (45, 54)

- Secondary prevention of sudden cardia death (45, 54)
    - Secondary prevention of cardiac arrest
    - Secondary prevention of sustained ventricular tachycardia
    - Coronary artery disease (if coronary revascularization is not possible)
    - Nonischemic dilated cardiomyopathy
    - Hypertrophic cardiomyopathy
    - Arrhythmogenic right ventricular Cardiomyopathy (ARVD/C)
    - Genetic Syndromes (e.g., Brugada Syndrome, long-QT Syndrome, short QT-Syndrome)
    - Syncope with inducible sustained VT
- Primary prevention of sudden cardiac death (45, 54)
    - Coronary artery disease (high-risk patients)
    - Nonischemic dilated cardiomyopathy (LVEF ≤ 35%, NYHA II or III)
    - Long-QT Syndrome (e.g., Romano-Ward Syndrome, Jervell and Lange-Nielsen Syndrome)
    - Hypertrophic cardiomyopathy (high risk patients)
    - Arrhythmogenic right ventricular Cardiomyopathy (ARVD/C)
    - Congenital Cardiomyopathy (e.g., Noncompaction of the left ventricle)
    - Primary Channelopathy (e.g., Brugada Syndrome)
    - Advanced heart failure and cardiac transplantation

1.3 Atrial High-Rate Episodes (AHRE)

Atrial high-rate episodes are the main topic of this diploma thesis. The term AHRE describes a relatively new discovered arrhythmia due to improvements in CIED technology over the past few decades.

1.3.1 Definition

The current definition of Atrial high-rate episodes describes these episodes as tachyarrhythmias detected by CIED`s with an atrial electrode. Usually, the minimal heart rate to detect AHRE is set as ≥ 175 or ≥ 180 bpm, while the minimum duration in most studies is ≥ 5 or ≥ 6 min. Visual confirmation by a clinician is needed to confirm the results protocolled by the CIED and to eliminate eventual electrical artifacts. The term subclinical atrial fibrillation is often used as a synonym for visually confirmed atrial high-rate episodes. (21, 58)

1.3.2 Epidemiology

Recent studies have shown that atrial high-rate episodes have been detected in 20 to 70% of all CIED patients (59-62). These are highly varying, depending on whether the patient previously suffered from clinical atrial fibrillation or not (63). Unfortunately, AHRE-detection in the general population is currently inaccurate due to the missing ability to perform long-term ECG monitoring. Still, the estimated incidence is believed to be significantly lower in the general population compared to CIED-patients (58, 64). However, due to still limited evidence, further studies are required to optimize management, risk stratification and to get a better knowledge concerning the progression to atrial fibrillation and adverse events (e.g., stroke). (21, 58)

1.3.3 Criteria to describe atrial high-rate episodes

Relevant criteria currently used in studies to describe AHRE:

Occurrence of episodes
Count of episodes during monitored timespan
Total duration during monitored timespan
Duration of the longest episode

Table 7 - AHRE criteria

1.3.4 Diagnosis and Recommendations

The primary diagnostic tool to detect atrial high-rate episodes is continuous monitoring by an implanted device, such as a pacemaker or ICD. However, results received from CIED should always be verified visually by a clinician to rule out eventual false-positive episodes or artifacts. Another potential way of detecting episodes is ECG and 24h-Holter-ECG, although the detection rate is significantly lower compared to implanted long-term monitoring (62). Therefore, the recommendation issued by the "2020 ESC Guidelines for the diagnosis and management of atrial fibrillation" (21) implies a further evaluation after detection of AHRE, including risk stratification (e.g., CHA_2DS_2VASc-Score, HAS-BLED-Score), ECG monitoring, and cardiovascular assessment. Additionally, the attending clinician should ensure continuous follow-up to detect changes in the patient's condition or progression to atrial fibrillation at an early stage. (65)

Haeley et. al. conducted a clinical trial regarding AHRE and the risk of stroke in 2012 (66). The published results indicate that patients who experienced AHRE/subclinical atrial fibrillation during the trial, also suffer from a significantly higher risk of ischaemic stroke or systemic embolism. (66)

2 Aims and Hypothesis

2.1 Aim & Objectives of this Study

This prospective study aims to gather data concerning atrial high-rate episodes in patients with cardiac implantable electronic devices. The main focus lies on gathering epidemiological data and eventual risk factors leading to these episodes.

2.2 Hypothesis

Null Hypothesis:

There is no significant difference regarding risk factors, comorbidities, or medications between patients suffering from AHRE and those who are not.

Alternative Hypothesis:

There is a significant difference regarding risk factors, comorbidities, or medications between patients suffering from atrial high-rate episodes and those who are not.

3 Materials and Methods

3.1 Study overview

The study is designed as an observational monocentric trial conducted at the University Hospital Graz / Department of Internal Medicine / Division of Cardiology and approved by the ethics committee of the Medical University of Graz. This diploma thesis is part of an ongoing larger observational study. Written informed consent was provided by all patients who took place in this study. Inclusion and exclusion criteria were set as described in 3.3.1 and 3.3.2. Every included patient had to undergo a basement assessment (detailed description in 3.2) and a six-month follow-up assessment, as explained in 3.4. Patients with missing follow-up assessment were excluded during the analyses, as shown in Figure 9.

3.2 Ethics Statement

The ethics approval has been issued by the Ethics Committee of the Medical University of Graz. The number of the committee's vote is 29-229 ex 16/17.

3.3 Baseline Assessment

3.3.1 Inclusion Criteria

The following criteria were set as inclusion criteria for all pacemaker and ICD patients at the baseline assessment:

No atrial fibrillation during the baseline assessment
No probe revision during the last three months
Atrial stimulation rate < 50%
Mode switch rate < 50%

Table 8 - Inclusion criteria

3.3.2 Exclusion Criteria

The following criteria were set as exclusion criteria for all pacemaker and ICD patients at the baseline assessment:

Patients with a pacemaker malfunction
Atrial fibrillation during the baseline assessment
Permanent atrial fibrillation
Insufficient data

Table 9 - Exclusion criteria

3.3.3 Pacemaker

The first part of the baseline assessment was the collection of recorded data concerning atrial high-rate episodes and other arrhythmias from the implanted pacemaker or ICD and the retrieving of basic information about the devices like manufacturer, placement of the probes for sensing and stimulation, and possible malfunctions of the devices. (Attachment Appendix Case Report Form)

3.3.4 Medical History

This part of the baseline assessment was performed as a structured interview with standardized questions. The height and weight of the patient were enquired or measured. The next step was to obtain information about the past medical history as well as the current medication with special attention for cardiac and vascular diseases or medications. Another part of the anamnesis is the evaluation of the CHA2DS2-VASc-Score (37) as well as the HAS-BLED-Score (38).

Missing diagnoses of the past medical history and current medications were obtained with the help of the MEDOCS-Software (the communication and information software of Styrian hospitals). The acquired information was noted on the data form for the baseline assessment (Attachment Appendix Case Report Form). Afterwards, the data was pseudonymized and safely stored in a database for further analyses.

3.3.5 24h-ECG

Another part of the baseline assessment is the patient's monitorization over 24h with a Holter ECG at home. During this 24h-period, the patient is allowed to resume his/her regular daily routine with only a few restrictions. A cardiologist reviewed the findings, and the approved data is also safely stored and pseudonymized on a database for further statistical analyses.

3.4 Follow Up

The Follow-up assessment took place six months after inclusion during the baseline assessment. The two main parts of this assessment were a structured anamnesis and the retrieving of information and events over these past six months from the implanted pacemaker or ICD.

3.4.1 Medical History

The first part of the follow-up assessment was another structured interview with the patient. The focus lay in hospitalizations, pacemaker malfunctions and cardiovascular adverse events during the last six months. Missing information about diagnoses and medications was obtained with the help of the MEDOCS-Software. (Attachment Appendix)

3.4.2 Pacemaker

The final pacemaker appointment was performed in combination with the follow-up anamnesis. The central part of this procedure was the analysis of the pacemaker event storage by an experienced cardiologist during the routine check-up of the pacemaker.

3.5 Statistical Analysis

Statistical analyses of the gathered data were performed using SPSS Statistics Version 27.0 (IBM, Armonk, NY). Initially the characterization of the study population was conducted with descriptive statistics.

Tables and diagrams were created by using SPSS Statistics Version 27.0 (IBM, Armonk, NY) and Microsoft Excel (Version 16.52) tools.

4 Results

4.1 Study Population

This monocentric study was conducted at the Department of Internal Medicine (Division of Cardiology) of the University Hospital Graz. In total, 42 patients were included from 2018 to 2020. However, 12 of these patients were excluded after the baseline assessment after having missed the follow-up assignment, while 30 patients were further analysed in this trial (Figure 9 - Strobe Chart). This population consists of 16 female and 26 male patients with an implanted cardiac electric device. The mean age in this patient group during the baseline assessment was 76,88 (±7).

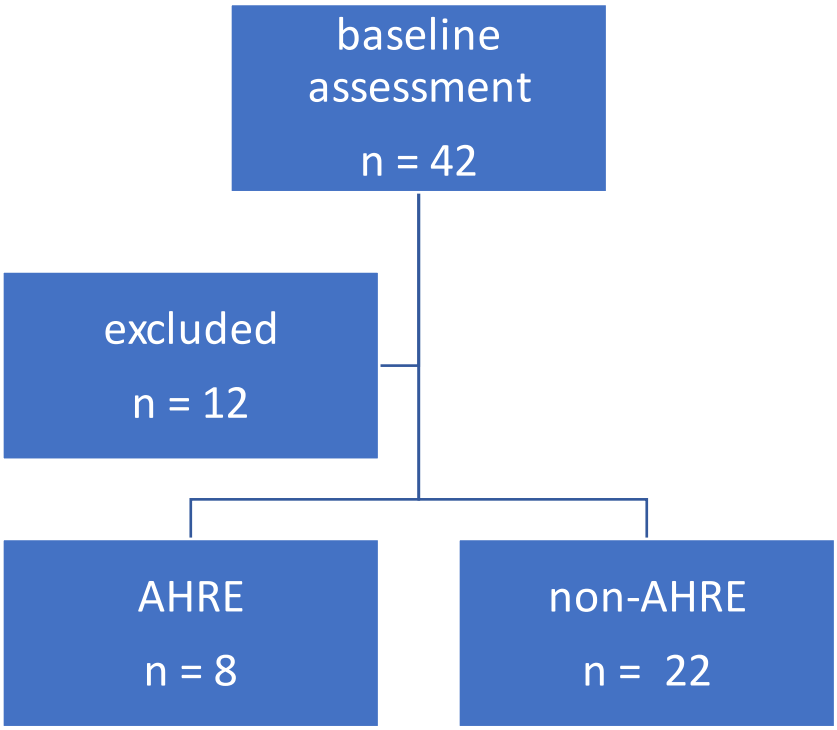

Figure 9 - Strobe Chart

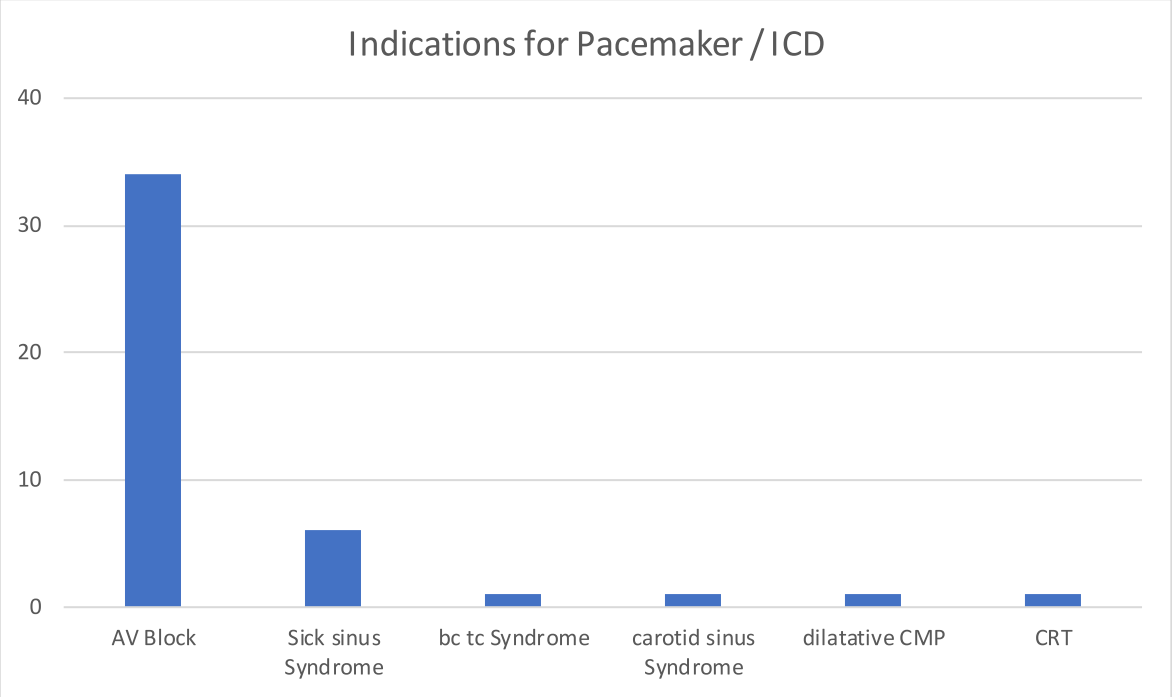

Figure 10 - Indications or Pacemaker / ICD

Every implanted device included in this trial contains an atrial lead to monitor the atrial rate. Concerning the given indications for pacemaker or ICD implantation (Figure 10), the by far most common one is AV block (34 patients), followed by Sick sinus syndrome (6 patients) and less common indications like tachycardia-bradycardia syndrome (1 patient), carotid sinus syndrome (1 patient), dilatative cardiomyopathy (1 patient) and cardiac resynchronization therapy (1 patient). Due to multiple indications in two patients, the summarized number exceeds the patients included in this trial. Programmed modes of operation in this trial cover DDD (97,6%) and AAI (2,4%).

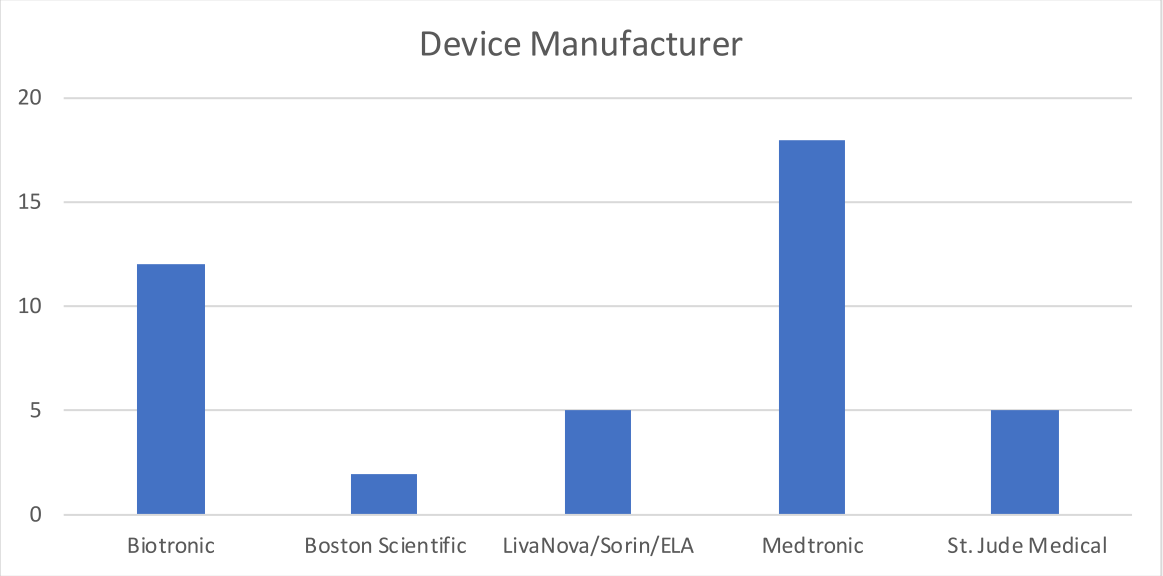

Figure 11 - Device Manufacturer

As shown in Figure 11, various manufacturers are currently producing pacemakers and ICD. This knowledge concerning the implanted device is essential due to varying atrial rate limits depending on the manufacturer's implanted device and programmed limit (170 to 200 bpm).

4.2 Baseline Assessment

Table 10 gives a brief overview of the main characteristics concerning the study population during baseline assessment. Atrial high-rate episodes were detected in 16 out of 42 patients. Therefore, the prevalence of AHRE in this study population during the baseline assessment is 38,1%.

Furthermore, Table 10 compares the non-AHRE and AHRE groups in CHA_2DS_2VASc-score, comorbidities, and medications. Significant differences between these two groups were detected by using the Fisher exact test at a CHA_2DS_2VASc-score > 4 (p-value 0,038) and antiarrhythmics class II (p-value 0,001). A history of clinical atrial fibrillation, on the other hand, is not significantly related to the development of atrial high-rate episodes. 24h-Holter-ECG as a diagnostic instrument for AHRE-detection documented subclinical atrial fibrillation in two patients.

	Total n = 42	non-AHRE n = 26	AHRE > 5min n = 16	p-value
Sex female	16 (38,1%)	10 (38,5%)	6 (37,5%)	0,606
Age	76,88 ±7,09	75,65 ±7,24	78,88 ±6,55	0,146
BMI	26,73 ±4,58	27,58 ±5,16	25,27 ±2,99	0,121
CHA_2DS_2VASc				
CHA_2DS_2VASc	3,62 ±1,1	3,38 ±0,9	4 ±1,32	0,124
$CHA_2DS_2VASc > 2$	35 (83,3%)	21 (80,8%)	14 (87,5%)	0,690
$CHA_2DS_2VASc > 3$	23 (54,8%)	13 (50%)	10 (62,5%)	0,530
$CHA_2DS_2VASc > 4$	8 (19%)	2 (7,7%)	6 (37,5%)	0,038
Comorbidities				
Diabetes	12 (28,6%)	8 (30,8%)	4 (25%)	0,740
CHF	4 (9,5%)	2 (7,7%)	2 (12,5%)	0,628
Hypertension	33 (78,6%)	19 (73,1%)	14 (87,5%)	0,442
vascular Disease	8 (19%)	5 (19,2%)	3 (18,8%)	1,000
stroke, TIA, thromboembolism	7 (16,7%)	3 (11,4%)	4 (25%)	0,397
History of atrial Fibrillation	5 (11,9%)	1 (3,8%)	4 (25%)	0,061
Medication				
acetylsalicylic or P2Y12 Inhibitor	15 (35,7%)	11 (42,3%)	4 (25%)	0,330
Anticoagulation	11 (26,2%)	4 (15,4%)	7 (43,8%)	0,070
Antihypertensives	33 (78,6%)	19 (73,1%)	14 (87,5%)	0,442
Antiarrhythmics Class II	18 (42,9%)	6 (23,1%)	12 (75%)	0,001
Others				
AF (Holter ECG)	2 (4,8%)	0 (0%)	2 (14,3 %)	0,123
History of Heart Surgery	6 (14,3%)	3 (11,5%)	3 (18,8%)	0,658
Coronary Artery Disease	13 (33,3%)	7 (30,4%)	6 (37,5%)	0,736
History of PCI	7 (16,7%)	4 (15,4%)	3 (18,8%)	1,000
History of Thrombosis	1 (3,3%)	1 (3,8%)	0 (0%)	1,000
History of Pulmonary embolism	2 (4,8%)	0 (0%)	2 (14,3 %)	0,123

Table 10 - Baseline Assessment

4.3 AHRE

AHRE occurred in 16 patients during the baseline assessment, resulting in a prevalence of 38,01%, while throughout the six-month follow-up, 8 out of 30 patients (26,67%) suffered from AHRE. The median count of episodes at the baseline assessment was four episodes. This number slightly increased to 7,5 during follow-up. Furthermore, none of the observed patients showed AHRE related symptoms neither during baseline nor follow-up assessment.

4.4 Follow-up assessment and adverse events

Initially, 42 patients were included in this trial, while 30 of these patients underwent the six-month follow-up assessment. Two of these patients needed a hospitalization during the six-month trial. None of the hospitalizations were due to an underlying cardiovascular cause. Between the baseline assessment and the six-month follow-up assessment, no patient suffered from a TIA, stroke, or other cardiovascular events.

5 Discussion

New technological advances regarding pacemaker and ICD devices over the past few decades led to the detection of atrial high-rate episodes (AHRE). However, there is currently a controversy in clinical trials concerning epidemiology, progression to clinical atrial fibrillation, and eventual adverse events.

Like other studies over the past few years (e.g. RATE Registry (60), Shanmugam et al. (61)), this clinical trial focuses on an unselected group of CIED-patients. The ASSERT trial published by Hohnloser H. S. et al (59) and similar studies, on the other hand, differ from this trial by only including patients selected by comorbidities or other criteria.

The statistical analysis of the gathered data revealed a prevalence of atrial high-rate episodes in CIED-patients around 38,1% during baseline assessment and 26,7% during six-month follow-up evaluation. These results are in line with the majority of previously published studies, as shown in Table 8. For example, the ASSERT trial published by Hohnloser H. S. et al (59) suggests a prevalence of 10,1% within three months after device implantation and 24,6% during follow-up.

Clinical Trial	Prevalence of AHRE
ASSERT (59)	24,6%
Shanmugam et al. (61)	39,8%
RATE Registry (60)	48% - 52%
Healey et al. (66)	10,1%
A-HIRATE (63)	53,8%

Table 11 - Prevalence of AHRE

Unlike Healey et al. (66), a correlation between the occurrence of AHRE and increased risk of stroke or systemic embolism has not been detected during this trial. A possible reason for this discordance between these two clinical studies could be the relatively small study population of 30 patients during the follow-up% in this trial compared with 2580 patients enrolled by Healey et al. in 2012 (66).

A significant difference between the non-AHRE and AHRE-group has been detected by a CHA_2DS_2VASc-Score above 4, leading to the assumption that patients with higher CHA_2DS_2VASc-Scores may have a higher risk of developing AHRE.

A median of four atrial high-rate episodes was recorded at the baseline assessment. This number slightly increased to 7,5 episodes during follow-up six months later. Furthermore, none of the participating patients presented AHRE related symptoms neither during baseline nor follow-up assessment. Therefore, zero patients developed symptomatic AF during this trial.

Implanted devices detected AHRE in 16 out of 42 patients while 24h-Holter-ECG, on the other hand, detected episodes of atrial fibrillation in two patients during baseline assessment. Therefore, reflecting the superiority of CIED regarding the detection of AHRE.

In Summary, this clinical trial confirms that AHRE is a common phenomenon in CIED-patients, while the therapeutical significance still remains unknown. Furthermore, patients with a high CHA_2DS_2VASc-Score (> 4) have a significantly higher risk of developing atrial high-rate episodes. Additionally, 24h-Holter-ECG showed a significantly lower detection rate than CIED memory analyses regarding AHRE, suggesting implanted devices as the primary diagnostic tool.

5.1 Strengths

Strengths of this clinical study lie in the 24h-Holter-ECG installation and CIED storage analysis during baseline assessment, allowing the comparison of two diagnostic instruments for detecting AHRE as described above.

5.2 Limitations

Due to the small sample size of 42 people included in the baseline assessment and 30 patients participating in the six-month follow-up assessment, there was no statistical correlation between AHRE and adverse events. However, a larger sample size could lead to more significant results.

Another limitation regarding the relatively small sample size occurred during statistical analyses of the AHRE related characteristics, leading to inconclusive results regarding the total duration, duration of the first episode, and duration of the longest episode. Therefore, these parameters were excluded from further analyses in this trial.

6 Conclusion

Based on the data gathered and analysed during this clinical trial, the prevalence of 38,1% during baseline assessment and 26,7% is in line with the majority of similar trials (Table 8). A significantly higher AHRE occurrence has been detected in patients with a CHA_2DS_2VASc-Score > 4, leading to the assumption that patients with higher CHA_2DS_2VASc-Score may have a higher risk of developing AHRE.

Correlation between AHRE and eventual adverse events (e.g., stroke, TIA, systemic embolism) has not been discovered during statistical analyses. A possible explanation for this missing correlation might be the small sample size. Therefore, further studies regarding this topic are required.

During this clinical study 24h-Holter-ECG and CIED storage analysis have been performed simultaneously, allowing the comparison of these two diagnostic instruments for detecting AHRE. This comparison confirmed the superiority of CIED regarding the detection of AHRE.

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8 Appendix

8.1 Case Report Form

SAFE-ME Studie Case Report Form V1.0 28.11.2018

Patientenetikett

Datum: _____

Patienten-ID: _____

Telefonnummer: _____

Investigator: _____

Einschlusskriterien	**Ausschlusskriterien**
□ Bei Abfrage im SR/Pacing (KEIN AF) □ letzte Sondenrevision vor > 3 Monaten □ Atriale Stimulationsrate:_____% (<50) □ ModeSwitch Rate: _____% (<50)	□ Schrittmacherfehlfunktion □ AF während Abfrage □ Permanentes AF
CHA_2DS_2-VASc Score (≥ 2!) □ Herzinsuffizienz □ Arterielle Hypertonie □ Diabetes mellitus □ Insult, TIA, Thrombembolie (x2) □Gefäßerkrankung(pAVK/Aorta/Carotis) □ Alter ≥ 65 Jahre □ Alter ≥ 75 Jahre	**HAS-BLED Score** □ Unkontrollierte Hypertonie (sys>160) □ Abnorme Nierenfunktion □ Abnorme Leberfunktion □ Insult □ Blutung in Anamnese/Prädisposition □ Labile INR-Werte □ Medikamentenabusus □ Alkoholabusus
Größe / Gewicht Größe: _____ cm Gewicht: _____ kg	**Blutdruck** systolisch: _____ mmHg diastolisch: _____ mmHg
Anamnese □ AF □ angeborene Herzerkrankung □ KHK □ pAVK □ cAVK □ Demenz □ Thrombose □ Z.n. PCI □ Thrombose □ Herzchir. Eingriff □ PAE □ ICB weitere:	**Eigenmedikation** □ Antikoagulation: □ ASS: □ Antiarrhythmika: □ Antihypertensiva: □ weitere:
□ **Holter angelegt**	**Termin in 6 Monaten**:

Zusatz 1: Labs	**Zusatz 2: Echo**
□ für Blutbank abgenommen □ ntProBNP: _____ pg/mL □ CRP: _____ mg/L □ Kreatinin: _____ mg/dL	Echo durchgeführt: □ heute / □ _____ LV-Funktion: □ gut / □ leicht / □ mittel / □ schwer reduziert LAMM (kurze Achse): _____ mm LA (4K): _____ mm RA (4K): _____ mm LA Fläche: _____ cm² E/E': _____ LVEDD: _____ mm
Device-Details Device-Typ: □ SM □ ICD Firma: _____ Typ: _____ Indikation: _____ letzte Device-Revision: _____ letzte Sondenrevision: _____ AHRE-Cutoff: _____ /min (soll:180) R-Sensor: □ an □ aus ventrikulärer Rhythmus: □ intrinsisch □ stimuliert vent. Stimulationsrate: _____ % Anzahl AHRE-Episoden: _____ Längste AHRE-Episode: _____ Anzahl AES/24h: _____ □ nsVT □ VT □ ATPs: _____ □ Schocks: _____ Weiteres:	**Follow Up Visite** Datum: _____ ModeSwitch-Rate: _____ % ventrikulärer Rhythmus: □ intrinsisch □ stimuliert vent. Stimulationsrate: _____ % Anzahl AHRE-Episoden: _____ Längste AHRE-Episode: _____ Anzahl AES/24h: _____ □ nsVT □ VT □ ATPs: _____ □ Schocks: _____ Weiteres: **Adverse Event:** □ Hospitalisierung □ kardiovaskuläre Hospitlaisierung □ Insult □ TIA □ Tod Details: