Gender differences regarding the complications in elderly patients with atrial fibrillation ablation

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UNIVERSITY OF SPLIT

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Diploma Thesis

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List of Abbreviations

AP= action potential

AV node =atrioventricular node

AVNRT = AV Node reentry tachycardia

CA= catheter ablation

CRT = cardiac resynchronization therapy

f= female

Hx of= History of

ICD = implantable cardioverter defibrillator

IVC= Inferior vena cava

LA= left atria

LAD = left anterior descending artery

LV= left ventricle

LXC= left circumflex artery

m= male

NS= Not significant

NYHA = New York Heart Association

PM= Pacemaker

PV-ablation= Pulmonary vein ablation

RA= Right atria

SVC= Superior vena cava

RV = right ventricle

SA node = sinoatrial node

SVC= Superior vena cava

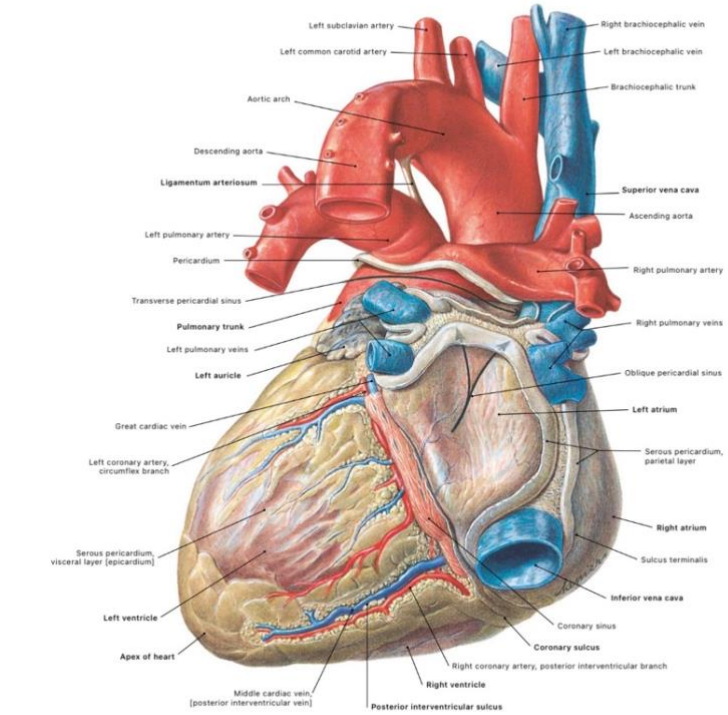
TMP= transmembrane potential

CHA_2DS_2-VASc Score= congestive heart failure, hypertension, age (>65= 1 poin, >75 = 2 points) diabetes, previous stroke/ Transient ischemic attack (2 points) and VASc stands for vascular disease (peripheral atrial disease, previous myocardial infarction, arteriosclerotic plaque) and sec category (female gender)

1.INTRODUCTION

1.1 Basic anatomy of the heart

The heart connects the pulmonary circulation and the systemic circulation, and is located in the middle mediastinum. The organ consists of four chambers (Figure 1); two atria and two ventricles (1,2). The right atria (RA) receives deoxygenated blood from the superior vena cava (SVC), the inferior vena cava (IVC) and the coronary veins. It pumps the deoxygenated blood through the tricipital valve into the right ventricle (RV) and from there the blood is conveyed through the pulmonary valve into the lungs. Here it is oxygenated and flows to the left atria (LA) via the pulmonary veins. The LA conveys the blood through the mitral valve into the left ventricle (LV) which is responsible for transportation of oxygenated blood through the aortic valve to the body (1-3). The four heart valves ensure the flow of blood in one direction. After leaving the LV oxygenated blood passes through the coronary arteries which arise from the root of the aorta and supply the myocardium and endocardium (1-3). Major branches of the left coronary artery are the left anterior descending artery (LAD) and the left circumflex artery (LXC) which mostly supply the left side of the heart and the anterior two thirds of the intraventricular septum. The right coronary artery branches into the right marginal artery, posterior descending artery, atrioventricular nodal artery, and sinoatrial artery. The right branches mostly supply the right side of the heart, the posterior aspect of the septum and the sinoatrial (SA) node and the atrioventricular (AV) node (1-3). The coronary sinus is the largest vein of the heart collecting all the deoxygenated blood and empties into the right atrium (1-3). The pericardium is the fibroserous sac enclosing the heart, consisting of an outermost layer and an innermost layer; the fibrous pericardium and the serous pericardium respectively. The microscopic anatomy of the heart consists of three layers, epicardium, myocardium, and endocardium. The parietal layer is the outermost layer of the serous pericardium. It is separated from the visceral layer of the serous pericardium, also known as epicardium, by the pericardial cavity containing pericardial fluid (1-3). The myocardium is the middle layer of the heart which is composed of fibroblast, extracellular matrix, and cardiomyocytes which are straited muscle cells. The myofibrils within the cardiomyocytes are organized into sarcomeres, building the smallest functional contractile unit. The endocardium is the innermost layer of the heart which is composed of three sublayers subendocardium, loose connected tissue and endothelium. The subendocardium the outermost layer of the endocardium is composed of loose connected tissue, cardiac Purkinje cells, veins, and nerves (1-3).



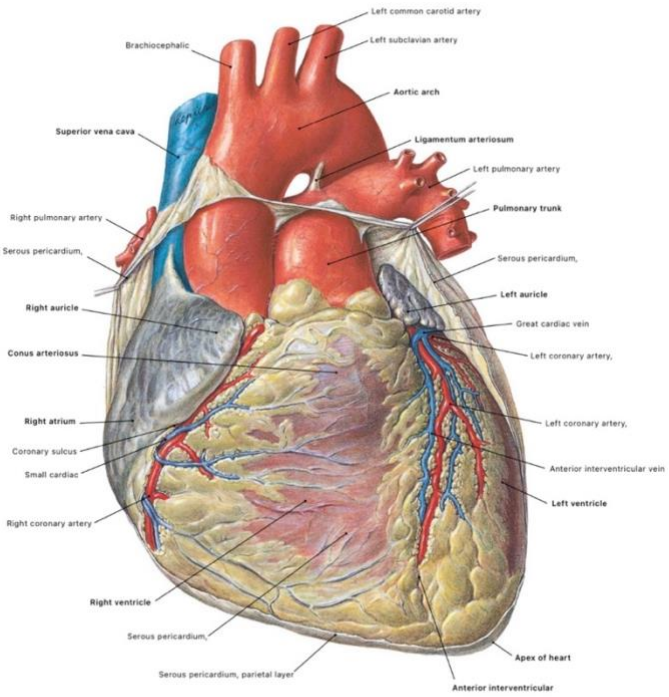


Figure 1 Schematic view of the heart
Source: Paulsen F., Waschke J. Sobotta Atlas of Human Anatomy 15th edition, Urban& Fischer: 2013

1.2 Electrophysiology of the heart

The conduction system, composed of nodes and specialized conduction cells, is responsible for the coordinated contraction of the heart. The first electrical impulses are initiated through the SA node located in the right atrium (1,2). These cardiac pacemaker cells spontaneously and autonomously generate an action potential (AP) from where it is transmitted to the AV node within the AV septum. Two bundles emerge after the AV node called bundle of His located within the ventricular septum. The conduction system ends in the subendocardium, and the nerve fibers are called the Purkinje fibers (2,3) (Figure 2).

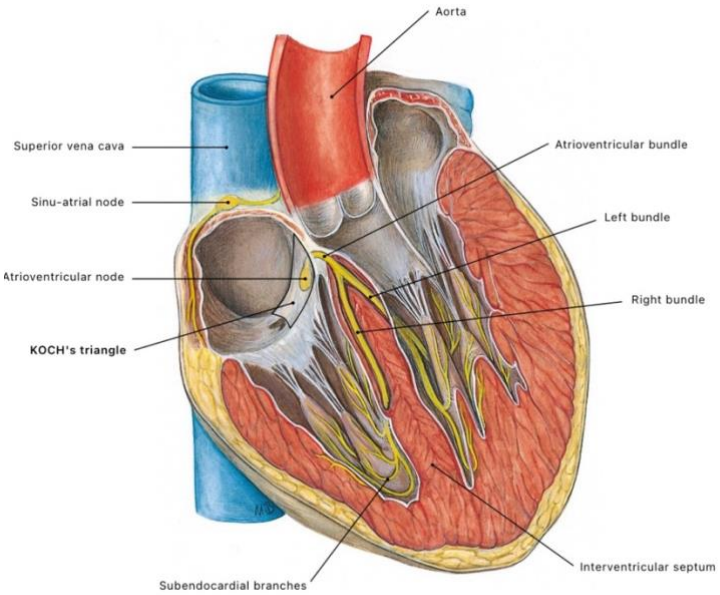


Figure 2 Schematic view of the conducting system of the heart
Source: Paulsen F., Waschke J. Sobotta Atlas of Human Anatomy 15th edition, Urban& Fischer: 2013

The cardiac action potential (AP) is structured in five phases (Figure 3). The AP starts with an upstroke in phase 0 which arises from the pacemaker cells (SA Node) causing the transmembrane potential (TMP) to rise above -90 mV. The funny channels in the pacemaker cells ensure spontaneous depolarization at the end of each repolarization and therefor the cells have no stable resting membrane potential. The pacemaker cells are responsible for the automaticity of the heart conduction system. The depolarization starts with the opening of fast voltage-gated Na^+channels at -65mV, which allows a rapid influx of sodium into the cells and

causes a further rise of membrane potential slightly above 0 mV. Phase 1 describes the early depolarization starting with the inactivation of the voltage- gated Na^+Channels and the opening of the transient K^+ channels returning the action potential to 0 mV. Phase 2 is the plateau phase, in which a potassium efflux through the delayed rectifier K^+ channels and calcium influx through L-type Ca^{2+}channels takes place. This triggers the release of Ca^{2+} from the sarcoplasmic reticulum and causes the contraction of the myocyte. Thus, the transmembrane potential is maintained just above 0 mV. Phase 3, the rapid repolarization, starts with the inactivation of the L-Type Ca^{2+} Channels, which were activated in the plateau phase. The continuous efflux of potassium through the delayed rectifier K^+channels lowers the TMP back to -90 mV. The sacrolemmal Na^+-Ca^{2+}exchanger and the Ca^{2+} −ATPase and the Na^+K^+-ATPase restore the normal transmembrane ionic concentration gradients by recreating the normal ion concentration. Phase 4, the membrane potential is stable at -90 mV, due to a constant outflow of K^+through the inward rectifier channels, and sodium and calcium channels are closed (2,3).

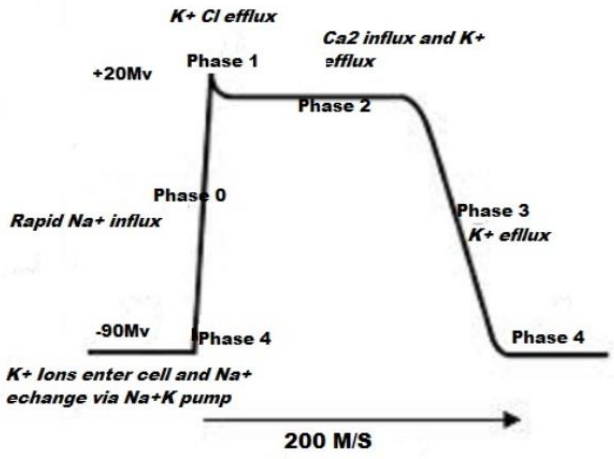


Figure 3 Schematic Action Potential of the heart
Source: Cardiac action potential [Internet]. Emergency Medical Paramedic 2010-1018. Available from: http://www.emergencymedicalparamedic.com/cardiac-action-potential/

1.3. Electrocardiography (ECG) and Gender Differences

The electrocardiography is a diagnostic tool, which is used to measure and record electrical conducting signals (2, 3). These signals are recorded as lines on graph paper and are shown as P wave, QRS complex and T wave. The P wave represents the depolarization of the atria originating from the SA- Node (Figure 4). The PR interval is the depolarization traveling from the SA Node to the AV node, His bundle and Purkinje fibers. The QRS complex represents the depolarization of the ventricle, which overrides the repolarization of the atria. The ST segment shows the time between depolarization and repolarization of the ventricle. The T wave is the repolarization of the ventricle, and the QT interval represents the total time of depolarization and repolarization of the ventricle. The interpretation of the amplitude and duration of the ECG allows a diagnostic of the normal cardiac physiology as well as the detection of cardiac arrhythmias, conduction system abnormalities or ischemia (2-4).

Comparing a standard ECG between the two different genders results in notable differences. The amplitude of the P- and T-wave, as well as the width of the QRS-complex are lower in women due to the smaller organ size than in men (5, 6). In general women have a higher frequency in the conducting system than men (6, 7). The conduction time between the SA node and the AV node also known as the PQ Interval, and the depolarization time of the ventricle is also shorter in female patients than in male patients (5, 6, 8). Whereas the repolarization representing the QT-Interval is slower and takes more time than in men (5-8). Women show an ST segment with a shallower slope and a less steep T wave, however while these characteristics can only be found in women, it is noticeable that young children regardless of their gender show the same PQ - and QT interval (5, 6). Therefore, it is assumed that the differences in the adolescence ECG could be due to the female sexual hormones. With the increasing age of women and men the QT interval increases in time (6).

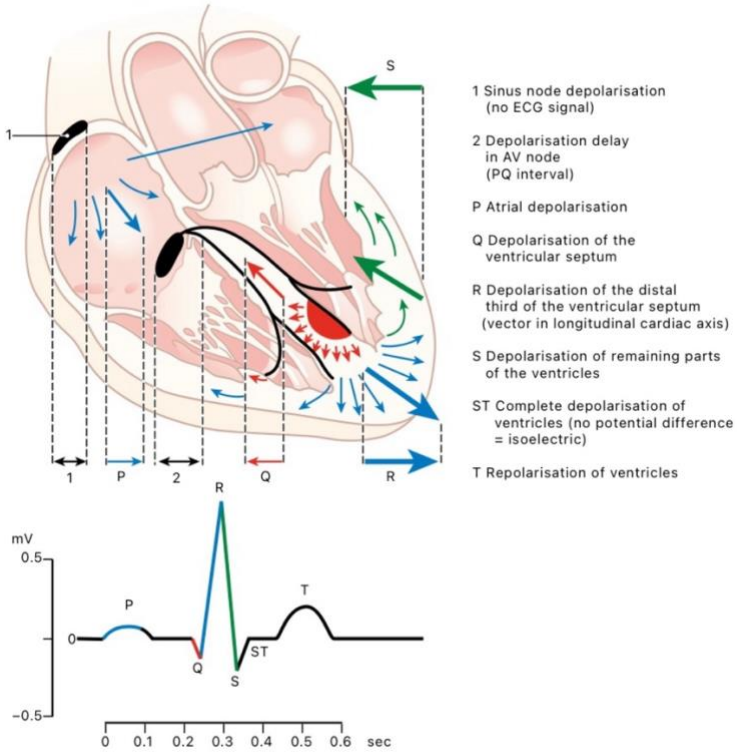


Figure 4 Schematic view of the conducting system of the heart and normal ECG
Source: Paulsen F., Waschke J. Sobotta Atlas of Human Anatomy 15th edition, Urban& Fischer: 2013

1.4. Cardiac Arrhythmia and Gender Differences

Cardiac arrhythmias are triggered by uncoordinated electrical impulses in the myocardium expressed by either accelerated, decelerated, or irregular heartbeats. While bradyarrhythmia is described as a heart rate slower than 60 beats per minute, tachyarrhythmia is defined as a heart rate faster than 100 beats per minute. The origin of tachyarrhythmias can either be supraventricular, triggered by an electrical impulse above the AV node or ventricular triggered by an impulse below the AV node. The supraventricular arrhythmias (SVT) either arise from abnormalities directly in SA Node, AV Node or conducting systems involving the myocytes in the atria (2, 9).

There are studies not only showing gender differences in the incidence and in the etiology of cardiac arrhythmias but also differences in the success rate of therapy and different methods of therapy (5).

Supraventricular arrhythmias (SVT) are a group of tachycardias arising above the ventricle either from abnormalities in pacemaker activities or the conducting systems involving the myocytes in the atria or the AV Node (10). Episodes of SVT may have a duration from seconds to hours (10). Different types of SVT are atrioventricular nodal reentry tachycardia (AVNRT), atrioventricular reciprocating tachycardia (AVRT), inappropriate sinus tachycardia, atrial flutter, and atrial fibrillation (AF) (10). All SVT episodes can be associated with symptoms like palpitations, dizziness, nausea, presyncope, anxiety, chest pain, diaphoresis, and syncope (10). In AVNRT and AVRT an accessory electrical pathway causing additional contractions throughout different parts of the heart, is active. While in AVNRT the accessory pathway can be found in the AV-Node and causes irregular contraction in the atrium and the ventricle in AVRT, the accessory pathway is mostly located in the bundle of Kent and causes renewed exaltation of myocytes in the atria. AV Node reentry tachycardia (AVNRT) and inappropriate sinus arrhythmia are the most common cardiac arrhythmias in women with more than two thirds of the patients being female and aged mostly between 30 and 50 years old (6, 8, 10, 11). Whereas AV reciprocating tachycardia (AVRT), Parkinson white syndrome, and atrial flutter are more often diagnosed in men who can be cured with a high success rate through catheter ablation (8, 10, 11). Nevertheless, there is a small but significant gender difference in success and complication rate (11). At the time of ablation female patients are much older than male patients and have suffered a longer time from typical symptoms like palpitations (5,12). They also describe higher reduction in quality of life than men due to psychological symptoms

like fear and depression (12, 13). These psychosomatic symptoms could be reasons why female patients are referred later to physicians and to the catheter ablation. (5, 10, 12).

Atrial fibrillation (AF) is the most common cardiac arrhythmia (12, 13, 14). It is defined as a rapid, irregular heart rate, causing uncoordinated ventricular responses which makes it impossible for the heart to pump the blood adequately in the arteries (2, 9). The sexual differences in the clinical presentation of atrial fibrillation and treatment have been stated in only a few publications and those studies have been predominantly on male patients (5, 12, 13, 15, 16). The incidence of AF increases with age in both genders thus more than 95% of patients with atrial fibrillation are over 60 years old (14). In general, men have a higher incidence of AF than women, although studies show an increased burden of the disease and an increased mortality with increasing age, the age adjusted mortality is higher in females than in males. (5, 7, 8, 13, 16, 17). Additionally female patients are often older when they are diagnosed with AF (5, 8, 12, 17). The etiology of AF is unknown, but there are several risk factors associated with an increased incidence (2, 9). The cardiovascular risk factors include advanced age, obesity, diabetes mellitus, hypertension, smoking, sleep apnea, intrinsic cardiac disorders and the body mass index in particular, making up the largest risk factor (2, 9, 16-19). Women are more frequently diagnosed with comorbidities like atrial hypertension, valve defects, diastolic heart failure and have a history of thyroid dysfunction and diabetes mellitus, while men on the other hand are more frequently diagnosed with coronary heart diseases like a previous myocardial infraction (5-8, 12, 13, 17, 19). While the exact pathophysiological mechanism remains unclear, the effects are sufficiently known. This mechanism can cause a burst of electrical activity throughout different areas in the atria and these can be autonomic foci near the pulmonary veins, atrial fibrotic tissue, or in an aberrant pathway causing a pre-excitation of the atria. These electrical activities could be due to volume overload causing hemodynamical stress, atrial ischemia, inflammation of the atrial myocardium or an altered ion conduction (2, 9, 19). New onset AF causes electrical modeling in the atria and if the AF persists it causes structural remodeling like atrial fibrosis and dilatation. The electrical and structural remodeling increases the incidence and susceptibility for AF thus creating a vicious cycle (2, 9, 19). While most individuals with AF are asymptomatic, some individuals might develop symptoms as palpitations, dizziness, nausea, presyncope, anxiety, chest pain, diaphoresis, and syncope (10). Some of those symptoms like dyspnea, chest pain, and fatigue are found equally in both genders, however female patients with atrial fibrillation often develop more severe symptoms and are associated with a worse prognosis (5, 10, 12, 20, 21). Those symptoms mostly include a higher ventricular response rate, longer episode of duration or more severe reduction of

quality of life (5, 8, 22). Similar to women with AF, women with AVNRT and AVRT also describe a higher reduction in quality of life than men due to psychological symptoms like fear and depression (5, 10, 12, 13 23). Furthermore, women are often later referred to a physician for treatment like catheter ablation, so they already developed a persistent form of atrial fibrillation with a more advanced remodeling (13, 21, 23). The late referral could be due to the psychosomatic presentation of the symptoms or due to the increased concern about their treatment (10, 12, 13). Long standing AF can cause complications like acute left heart failure, pulmonary edema and thromboembolic events like stroke or TIA, renal or splenic infraction or life-threatening ventricular tachycardia (2, 9). The initial diagnosis is done with an electrocardiography (ECG) (24, 25). Typically, ECG findings in AF show irregular RR intervals and also may include a complete AV dissociation (Figure 4). The heart rate is mostly tachycardia with more that 100 beats per minute while the atrial rate exceeds the ventricular rate. The P-Waves are indiscernible and instead fibrillation waves are seen at a rate of 300-600 beats/minutes and PR intervals are not distinguishable. Mostly the QRS complex is more narrowed, however a broader QRS complex might be seen in patients with a bundle branch block or a complete AV block with a ventricular escape (4).

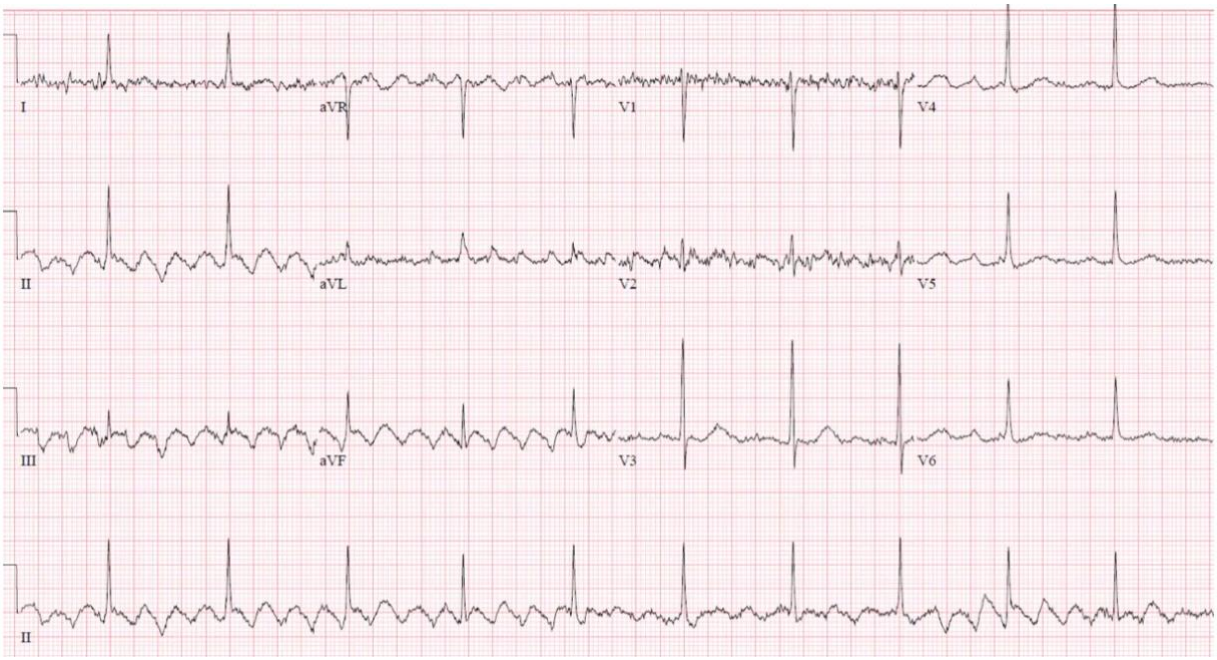


Figure 5 ECG Atrial Fibrillation
Source*:* Approach to Atrial fibrillation [Internet]. McLaren J. ECG Cases 28. 2022 Feb. 28th Available from: https://emergencymedicinecases.com/ecg-cases-approach-atrial-fibrillation/

There are various complications due to AF (13). The most severe complication can be thromboembolic event, like a stroke (5, 7, 12, 13, 17, 20, 21, 24-26). The CHA_2DS_2-VASc Score is a method to predict thromboembolic events in AF. CHA_2DS_2-VASc Score is an aberration for congested heart failure, hypertension, age diabetes, previous stroke/transient ischemic attacks and VASc stands for vascular diseases such as peripheral atrial diseases, pervious myocardial infarction, arteriosclerotic plaque, and sex category the female gender. Women and patients between the age 65-75 years are generally rated with a higher risk for a thromboembolic event in the CHA_2DS_2-VASc Score (5, 12, 17). Studies show that there is a correlation between AF and stroke in female patients, with at least 25%-30% of all patients with ischemic stroke have an underlying AF (13, 17, 26). Women suffer more frequently from permanent damage causing worse long-term outcomes (5). Several studies describe a reduced prescription rate of anticoagulation therapy to elder women compared to elder men (7, 12- 14). While there is no difference in gender regarding the success of preventive measures of thromboembolic events, the recurrency rate in females taking anticoagulation therapy was significantly lower than in males (5, 13, 24, 25). The treatment approach of AF is different in unstable and stable patients. The emergency approach in unstable patients is an electrical cardioversion, the method of applying direct current shocks of gradually increasing strength, which are administrated until the sinus rhythm is restored (2, 9, 19). The goal in stable patients is to control the heart rhythm and have the heart rate restored (2, 9, 19). Rate control is used to normalize the ventricular heart rate and to reduce the symptoms. The rate should be less than $\frac{110}{min}$ for asymptomatic patients and less than $\frac{80}{min}$ for symptomatic patients (2, 9). The rate control is the first line of therapy for chronic antiarrhythmic therapy including pharmacological options like beta blockers (e.g. metoprolol, atenolol, propranolol) or nondihydropyridine calcium channel blockers (e.g. diltiazem, verapamil) (10). In patients with a decompensated heart failure and a contraindication for beta blockers the second line therapy is digoxin and if all other treatment options fail amiodaron is the third line therapy (2, 9). Studies about the frequency of usage of antiarrhythmic therapy show mixed results (13). While some show that there is no gender difference in the frequency of usage of antiarrhythmic agents in AF, others do show a gender difference (5, 12, 13, 17, 20, 27). Beta blockers are more often prescribed to male patients whereas digoxin is more often prescribed to female patients, furthermore there is proof that antiarrhythmics of the class IA and III have a higher occurrence of side effects in women. (5, 12, 14). Class III antiarrhythmics (e.g. sotalol) are associated with a higher risk of development of polymorphic ventricular tachycardia in setting of prolonged QT interval e.g. Torsades de pointes (5-7, 13). These side effects could be due to the hormonal changes during

menstrual cycles (13). Women who receive rhythm control have a significantly higher risk of development of heart failure, thromboembolic events, bleeding and adverse effect from antiarrhythmic drugs and pacemaker implantation compared to women receiving rate control (6, 7, 26, 27). In men no difference between both methods of therapy can be found (7). The surgical options for rate control are either the AV nodal ablation or the implantation of a permanent ventricular pacemaker. Indications for the surgical treatment option would be recurrent AF and refractory AF to medical rate control, or for patients who do not tolerate any pharmacological options, (2, 9) moreover these procedures offer a permanent cure of AF (10). The goal of rhythm control in AF is the termination of AF and the restoration of sinus rhythm to prevent atrial remodeling and improve symptoms (2, 9). These procedures offer a permanent cure of AF (10). There are three different types of cardioversions in total. The electrical cardioversion is also the first line approach in an emergency, The second being the pharmacological cardioversion which can be either an administration intravenous or oral antiarrhythmics and the third cardioversion is the catheter ablation (CA). The catheter radiofrequency ablation or the maze ablation create scar tissue that prevents the spreading of ectopic impulses (2,9).

1.5. Cardiac catheterization and Gender Differences

Cardiac catheterization is a procedure which can be used as a diagnostic tool and a treatment approach in cardiovascular conditions (21). A catheter is inserted through the femoral artery, if the access is impossible then it is feasible via the radial artery or brachial artery, the coronary arteries or into the chambers (2, 9) (Figure 5). With the catheter it is feasible to evaluate blood supply to the cardiac muscle, open narrow coronary arteries with a stent, take tissue samples, open narrow heart valve via valvuloplasty or examine electrophysiological pathways (2, 9). The catheter uses heat or cold energy to create tiny scars in the heart tissue to block abnormal electrical foci or conduction and to restore a normal SA Rhythm (22). CA is able to correct supraventricular arrhythmia, for example atrial fibrillation or atrial flutter. It can also be used to place an intracardiac pacemaker or defibrillator (2, 9).

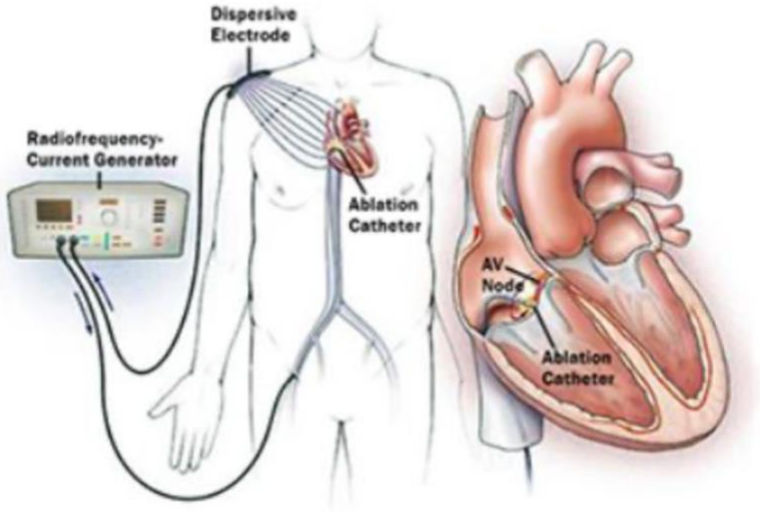


Figure 6 Schematic view of Catheter ablation
Source: Design of Radio-Frequency Ablation Catheter [Internet]. COMSOL Conference 2018. Available from: https://www.comsol.de/paper/design-of-radio-frequency-ablation-catheter-69501

In all studies regarding catheter ablation in patients with AF there are not enough female participants (5, 12, 17, 15, 22). Reasons for this gender difference is not quite sure yet, but it could be due to a later referral to a physician for catheter ablation or that women are more afraid of the invasive procedure (13). In general women were more frequently ablated with an SA rhythm and underwent more often an AV Node ablation (12). The overall procedure time with radiofrequency therapy was shorter in females than in males, one explanation could be the smaller LA than in men. (5, 22, 28). The success rate however in patients with catheter ablation with AF is contradictory, with some studies showing no gender difference and the majority of studies showing that women have a significantly reduced success rate than men (5, 6, 13, 17,

28). The female sex was associated with a higher long term recurrence rate after both radiofrequency and cryoballoon ablation therapy of AF (22). Causes are not exactly clear, but reasons could be the increased age of female patients, the late referral to a physician for CA and developed a persistent form of atrial fibrillation with a more advanced remodeling which could influence the outcome of the CA (5). The complication rate in female patients early after CA is also higher than in male patients, with possible complications due to cardiac ablations being divided into three groups (5, 6, 22, 23). The first group being major non-fatal complications like stroke, myocardial infarct, and major bleeding (22). The second being moderate complications like transient ischemic stroke (TIA), atrial fibrillation recurrence, resuscitation, peripheral vascular complications, third degree AV block, infection at the side of catheter insertion, phrenic nerve palsy, pneumothorax, hemothorax, pericardial effusion, pulmonary embolism, pulmonary vein stenosis, emergency cardiac surgery, endocarditis, sepsis, and atrio-esophageal fistula (22). The third group, minor complications, are defined as bleeding, which doesn't need any intervention, first and second-degree AV block or a new bundle branch block (22). In particular, hospital complications are significantly higher in the female sex (17, 22). There is a noticeably higher incidence of cardiac perforations and with a cardiac tamponade and access-site bleeding and hematoma in women than in men (5-7, 17, 22). A possible explanation could be the thinner wall of the LA due to the increased age of the women (5- 7, 22). Studies including a follow up after the CA showed that female patients had a higher risk of AF recurrency than male patients (17, 22). Women described more severe limitation in physical capacity as classified by NYHA states and experienced more frequent angina pectoris (22). Most patients received beta-blockers, however with a higher prescription rate in female patients (17, 22). Additionally, women were also more likely to receive digitalis as well as anticoagulation therapy (22). Overall women were less likely to receive a cardioversion or repeat ablation procedure but more pacemaker implantations were required by women (17, 22). Overall hospitalization was also higher in women compared to men especially the re-hospitalization due to AF (17, 22). Women were less likely to be re-hospitalized for myocardial infarction and were more likely to be admitted with congestive heart failure over the following year (17).

2. OBJECTIVES AND HYPOTHESES

2.1. Objective

The objective of this study is to confirm whether there is a connection between gender differences and the complications in elderly patients (patients over 70 years) with AF ablation. Additionally, this study aims to clarify if there is an increased recurrency of AF in women than in men in the one-year follow up.

2.2 Hypotheses

1. Elderly women have an increased complication rate early after the initial therapy.
2. Elderly women have an increased complication rate within the follow up year.

3.SUBJECTS AND METHODS

3.1. The German Ablation Registry

The Stiftung Institut für Herzinfarktforschung (IHF, Ludwigshafen, Germany) administrates the German Ablation Registry. The German Ablation Registry is a collaboration of 55 German centers (PI: Professor Brachmann, Coburg). These centers participated in collecting patient-specific and procedural data after a written consent (22)**.** In total the data of 995 patients receiving a CA of SVT were prospectively collected**.** The documentation was paperless, voluntary and was carried out on an internet-based case report. The IHF is responsible for the project development, management, and clinical monitoring.

3.2. Patient selection

This retrospective study used exclusively data from the German Ablation Registry. The study compared the complications and the complication rate between men and women after cardiac ablation in the time period from January 2007 January 2010 and a one year follow-up. The clinical data was acquired from those anonymized patient records (total: 995 patients; female: 455, male: 540) and procedural data which fulfilled the inclusion criteria. During the therapy patients were followed by telephone contact. Participants were to be questioned about palpitations, blood pressure, presyncope, syncope, therapy resistance with medications. This study was approved by the Internal Review Board of the Medical School REGIOMED.

3.2.1. Inclusion Criteria

The clinical data of this study included patients (total: 995 patients; female: 455, male: 540) over 70 years from the German Ablation Registry. The patients received a catheter ablation due to AF in the years January 2007- January 2010 with a one year follow-up. Only patients diagnosed with specific complications due to cardiac ablation after atrial fibrillation were included in the study.

3.2.2. Exclusion Criteria

Patients younger than 70 years were not included in this study as well as patients diagnosed with any other supraventricular tachyarrhythmia. Additionally, patients without complications will be only evaluated to determine the probability to develop any complications at all but not be included in the main analyses.

3.3. Ablation procedure

In most patients a catheter was inserted through the femoral vein to access the heart and to induce abnormal foci of electrical activity by direct contact or by isolating them from the rest of the atrium. The methods of catheter ablation were circumferential of segmental pulmonary vein ablation, linear ablation, or ablation of complex fractional atrial electrogram (Figure 6). The radiofrequency ablation was the preferred approach in both male and female patients, followed by cryoballoon ablation. Most patient underwent an analgesic sedation, none of the patients needed an endotracheal anesthesia.

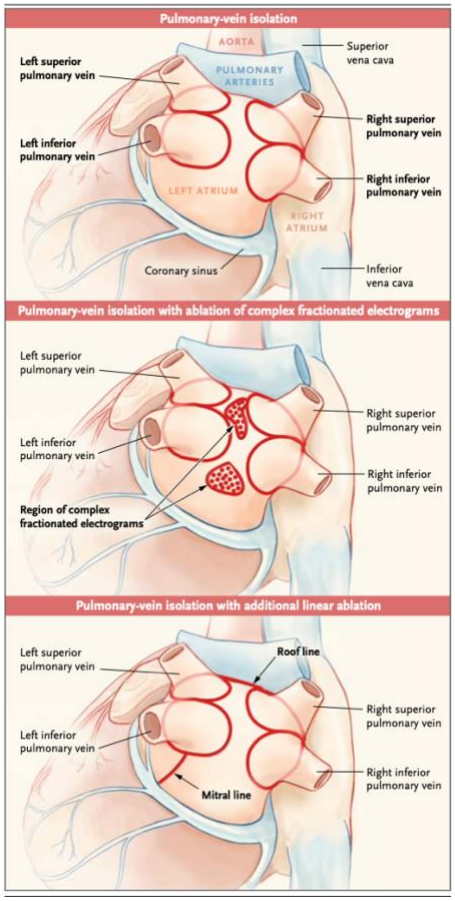


Figure 7 Schematic view of methods of Catheter Ablation
Source: Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R et al.: Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med 2015

3.4. Complications

In this study possible complications due to cardiac ablations are classified as minor, moderate and major complications. Minor complications are defined as bleeding which does not require any intervention, first and second-degree AV block or a new bundle branch block.

Moderate complications are transient ischemic attack (TIA), atrial fibrillation recurrence, resuscitation, peripheral vascular complications, third degree AV block, infection at the side of catheter insertion, phrenic nerve palsy, pneumothorax, hemothorax, pericardial effusion, pulmonary embolism, pulmonary vein stenosis, emergency cardiac surgery, endocarditis, sepsis, and atrio-esophageal fistula. Major non-fatal complications are described as stroke, myocardial infarction, and major bleeding.

3.5. Follow-up

The follow-up was performed by telephone by the Institut für Herzinfarkt Forschung (IHF) in Ludwighafen one year after the initial ablation. During the call the patients were asked if they experienced any adverse effects like myocardial infarction, stroke or embolic events, atrial fibrillation recurrence or if they noticed symptoms like palpitations, syncope and if they required another catheter ablation.

3.6. Statistical tests

The statistical computations are performed using the software package SAS release 9.4 (SAS Institute, Inc., Cary, North Carolina. U.S.A.). Observed binary or categorical data are presented as percentages and absolute counts. Continuous data are characterized by median, first and third quartile, mean and standard deviation. The number of available observations is given for each variable.

Probabilities of binary variables are compared using Pearson chi-square test; in case of infrequent events Fisher's exact test may be used. The normality of continuous distributions is tested by Kolmogorov-Smirnov test for all continuous variables. However, Wilcoxon-Mann-Whitney test is generally used for the comparison of continuous variables between patient groups. This test a rank-based procedure for the detection of a stochastic tendency between two independent samples. It does not require the variable to have a normal distribution, but only to be metrically or ordinally scaled. The P value was considered statically significant $P < 0.05$.

With regard to the hypothesized endpoints, which are all binary, effect measures are given in terms of odds ratios, with the variability of the estimation expressed as 95%-confidence intervals. For unifactorial comparisons asymptotic confidence intervals are calculated according to Woolf, in multivariable models Wald confidence intervals are calculated by logistic regression.

4. RESULTS

4.1. Gender differences in clinical characteristics of elderly patients before CA

Patient data including patients (total: 995 patients; female (f): 455(45.7%), male (m): 540 (54,3%)) over 70 years receiving a cardiac ablation after atrial fibrillation from January 2007- January 2010 with a one year follow-up. The median age for both sex is 73 years. 125 (27.5%) females and 122 (22.6%) males are older than 75 years (Table 1).

Table 1 Age and gender distribution of patients. (N=995)

AGE GROUPS	**TOTAL**	**FEMALE**	**MALE**	***P- Value* ***
Number of patients	995	455	540	NS
< 75	748	330	417	NS
>75	247 (24.8 %)	125 (27.5 %)	122 (22.6 %)	0.076
Medium Age	73.7 ± 3.7	74.1 ± 4.0	74.1 ± 4.0	**0.005**

Data are presented as absolute numbers. NS= Not significant: P > 0.05
*Pearson Chi^2 Test or Mann-Whitney-Wilcoxon Test. All significant P values are in bolt letters.

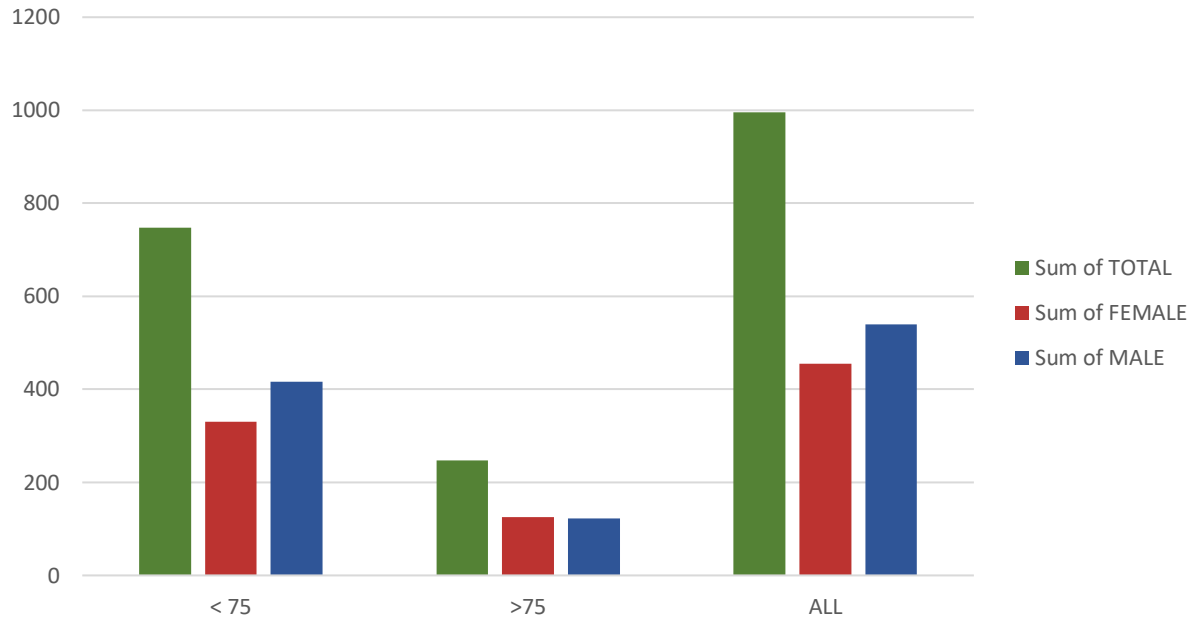


Figure 8 Age and gender distribution of patients. (N=995)

Male patients had a higher incidence of cardiac comorbidities like coronary artery diseases, prior myocardial infarct, cardiomyopathies, and a reduced left ventricular function compared to female patients (f: 48.4%, m: 58.9%, *P=<0.001*). Kidney insufficiency (f: 5.9%, m: 10,5%, *P=0.28*) was also more prevalence in male patients. Other comorbidities had a higher frequency in female patients for example arterial hypertension (f: 75.3%, m: 73.7% *P= 0.81*), diabetes mellitus (f: 13% m: 12.6% *P=0.86*), and stroke (f: 8.3%, m: 4.0% *P=0.26*) (Table 2).

Table 2 Comorbidities before catheter ablation

	TOTAL	**FEMALE**	**MALE**	***P- Value ****
Number of patients	100% (N=995)	45.7%	54.3%	NS
Diabetes Mellitus	12.8 % (127/995)	13.0 % (59/455)	12.6 % (68/540)	0.860
Kidney insufficiency	8.1 % (13/161)	5.9 % (5/85)	10.5 % (8/76)	0.280
Atrial Hypertension	74.5 % (120/161)	75.3 % (64/85)	73.7 % (56/76)	0.810
Stroke	6.3 % (10/159)	8.3 % (7/84)	4.0 % (3/75)	0.260
Chronic obstructive pulmonary disease	2.5 % (4/158)	2.4 % (2/84)	2.7 % (2/74)	0.900
Peripheral arterial disease	1.9 % (3/158)	1.2 % (1/83)	2.7 % (2/75)	0.500
Cardiac disease	54.1 % (538/995)	48.4 % (220/455)	58.9 % (318/540)	**<0.001**
Coronary artery disease	31.5 % (313/995)	21.5 % (98/455)	39.8 % (215/540)	**<0.001**
Myocardial infarctions	8.1 % (81/995)	5.5 % (25/455)	10.4 % (56/540)	**0.005**
Valvular disease	11.7 % (116/995)	12.3 % (56/455)	11.1 % (60/540)	0.560

Data are presented as percentages (%). In parenthesis, data is presented as absolute numbers. (Patients with comorbidities vs sample size) NS= Not significant: P > 0.05
*Pearson Chi^2 Test or Mann-Whitney-Wilcoxon Test. All significant P values are in bolt letters.

The amount of an implantable pacemaker, implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT) in the cohort was nearly the same between female (21,1%) and male patients (21,3%) *(P=0.94)* (Table 3).

Table 3 Implantation: Pacemaker/ Implantable cardioverter defibrillator (ICD)/ Cardio resynchronization therapy (CRT) before catheter ablation

	TOTAL	**FEMALE**	**MALE**	***P- Value ****
Hx of Impl. Pacemaker/ICD/CRT	211	96	115	0.940
Hx of Impl. pacemaker	171	88	83	0.100
Hx of Impl. ICD	30	7	23	**0.010**
Hx of Impl. CRT	26	5	21	**0.010**

Data are presented as absolute numbers. NS= Not significant: P > 0.05.
*Pearson Chi^2 Test or Mann-Whitney-Wilcoxon Test. All significant P values are in bolt letters.

Table 4 demonstrates the gender differences in the New York Heart Association (NYHA). NYHA states the physical capacity in patients with cardiac comorbidities, was slightly more pronounced in men.

Table 4 New York Heart Association Classification before catheter ablation

	TOTAL	**FEMALE**	**MALE**
Cardiac disease	54.1 % (538/995)	48.4 % (220/455)	58.9 % (318/540)
NYHA 1	44.4 % (239/538)	41.4 % (91/220)	46.5 % (148/318)
NYHA 2	43.5 % (234/538)	47.7 % (105/220)	40.6 % (129/318)
NYHA 3	11.0 % (59/538)	10.0 % (22/220)	11.6 % (37/318)
NYHA 4	1.1 % (6/538)	0.9 % (2/220)	1.3 % (4/318)
NYHA 2+	55.6 % (299/538)	58.6 % (129/220)	53.5 % (170/318)

Data are presented as percentages (%). In parenthesis, data is presented as absolute numbers.

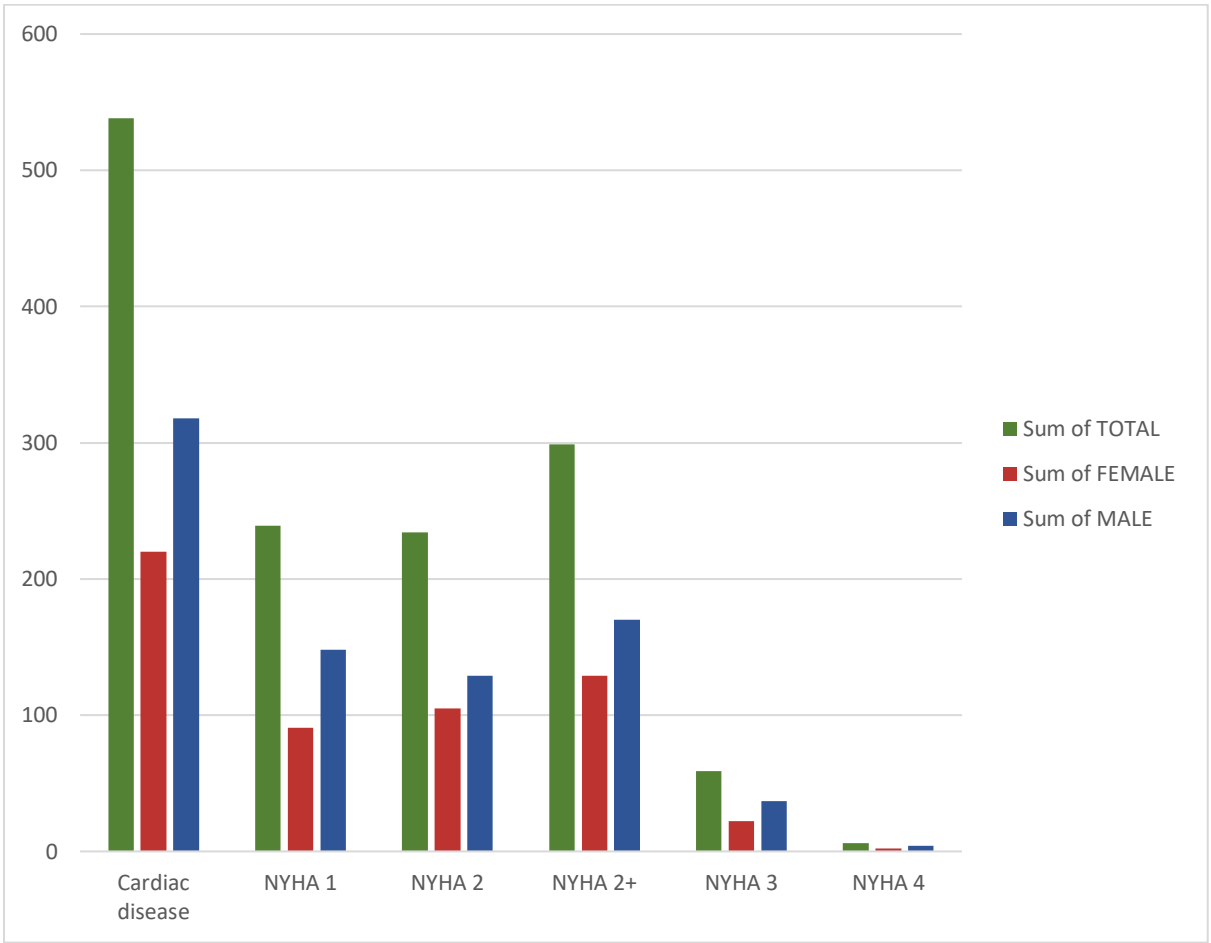


Figure 9 New York Heart Association Classification before catheter ablation

As seen in Table 5 nearly all patients (female: 98,5%, male: 98,1% *P= 0.7*) described palpitations occurring minimum once a month. Female patients noticed symptoms like presyncope more often than men (f: 2.2%, m: 0.4% *P= 0.053*) whereas men slightly more often

experienced a syncope (f: 1.5%, m: 1.7%, *P=0.87*). A resistance to antiarrhythmic therapy was presented in 87% of the female patients and in 90% of the male patients *(P=0.14)*.

Table 5 Symptoms before catheter ablation

	TOTAL	**FEMALE**	**MALE**	***P- Value ****
Palpitation	98.3 % (975/992)	98.5 % (447/454)	98.1 % (528/538)	0.700
Presyncope	1.4 % (14/992)	2.2 % (10/454)	0.7 % (4/538)	0.052
Syncope	1.6 % (16/992)	1.5 % (7/454)	1.7 % (9/538)	0.870
Reanimation	0.1 % (1/992)	0.0 % (0/454)	0.2 % (1/538)	0.360
Frequency of episode				
Once a month	90.6 % (887/979)	91.4 % (406/444)	89.9 % (481/535)	0.410
Once a year	9.2 % (90/979)	8.6 % (38/444)	9.7 % (52/535)	0.530

Data are presented as percentages (%). In parenthesis, data is presented as absolute numbers.
NS= Not significant: P > 0.05
*Pearson Chi^2 Test or Mann-Whitney-Wilcoxon Test. All significant P values are in bolt letters.

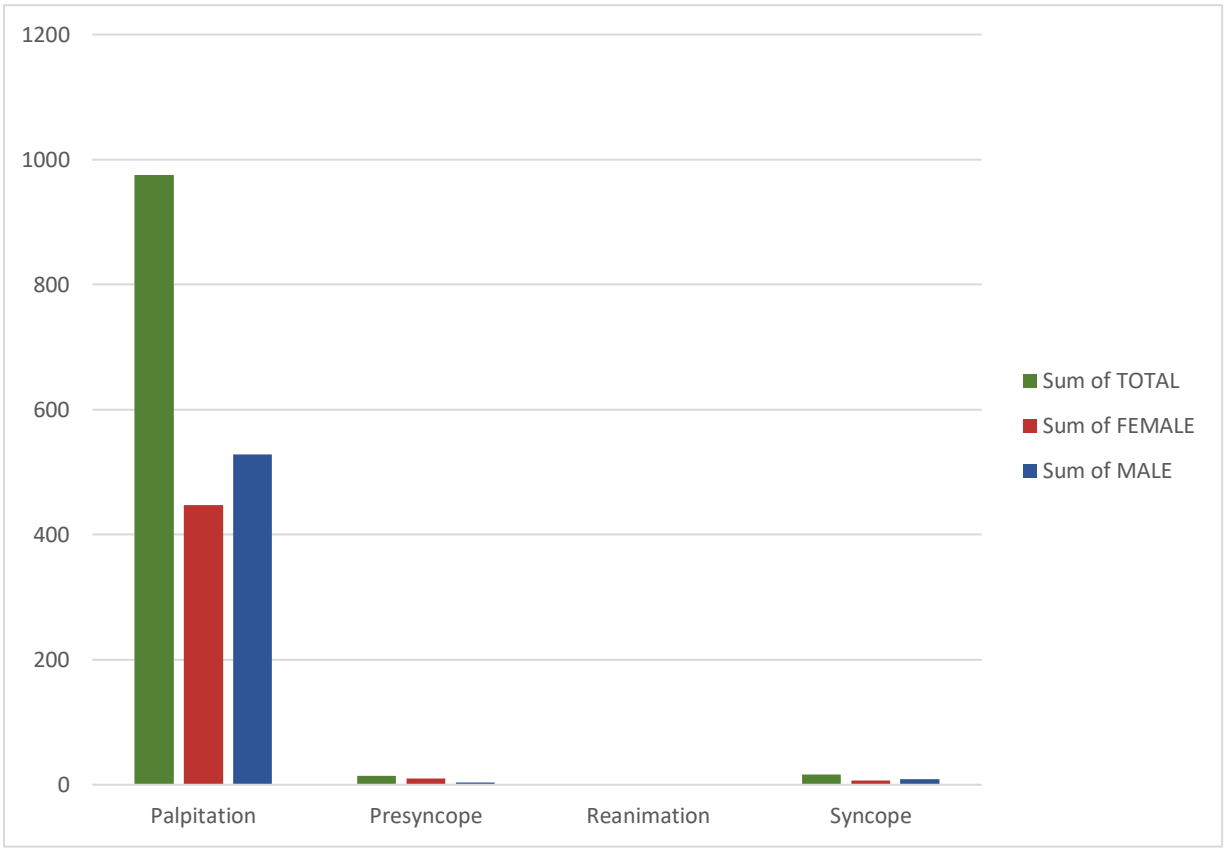


Figure 10 Symptoms before catheter ablation

The CHA_2DS_2- VASc-Score is a method to predict thromboembolic events in AF. CHA_2DS_2-VASc Score is an aberration for congested heart failure, hypertension, age (>65=1

point, >75= 2 points) diabetes, previous stroke/transient ischemic attacks (2 points) and VASc stands for vascular diseases (peripheral atrial diseases, pervious myocardial infarction, arteriosclerotic plaque) and sex category (female gender. In female patients the CHA_2DS_2-VASc-Score is significantly higher than in men (*P=<0.001*).

4.2. Gender differences during the procedure

All patients receiving a catheter ablation had a history of AF. The catheter ablation was performed during SA rhythm in 56.5% and during AF in 43.5%. 984 patients had one ablation during their hospitalization, 1% (9 females; 1 male) needed two catheter ablation and only one female patient received more than two ablations. Most patients underwent an analgesic sedation (81.3% Female, 86.1% male), 14.9% of the patients did not receive any sedation and none of the patients needed an endotracheal anesthesia. The radiofrequency ablation was the preferred method in both male and female patients (84.6% female, 86.1% male), followed by cryoballoon ablation (14.9%, female, 13.5% male). Most of the patients received circumferential PV-ablation (71.0% female, 76.5% male). Overall, the procedure-time was lower in the female cohort (1800 sec. female, 2340 sec. male, *P< 0,025*). There was no significant difference in the success rate. The procedure result was successful in 96.1% of the cohort (female 95.4%, male 96.7% *P= 0.30*). A partial success, in which not all the electrophysiological morphologies where ablated, was achieved in 2.2% of the female cohort and in 2.4% of the male cohort (*P=0.83*). No success after the catheter ablation was seen in eleven women and in five men (*P=0.062*).

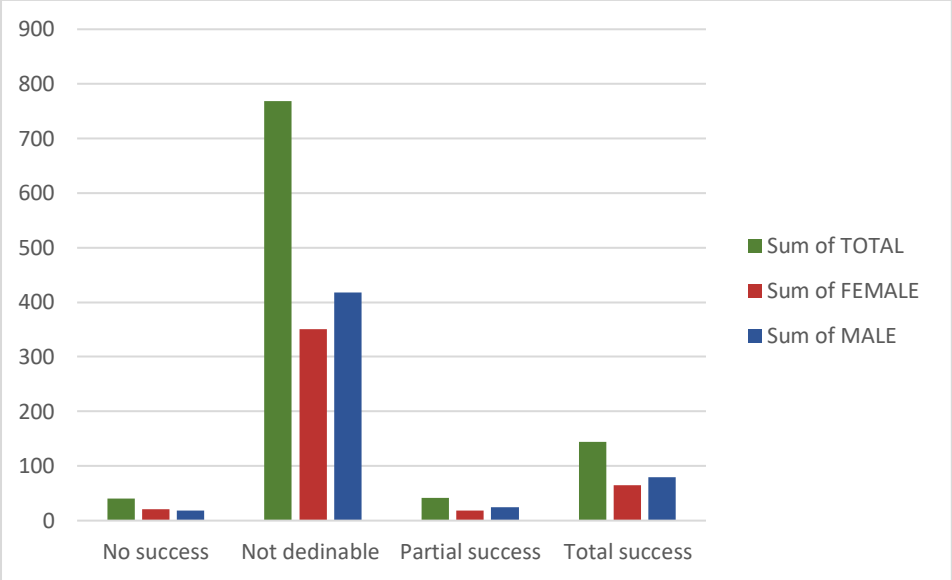


Figure 11 Success rate after catheter ablation

4.3. Gender differences in hospital complications

Periprocedural and postprocedural mortality was very low in both cohorts. Only one female died from an unknown cardiovascular cause. Overall non-fatal complications occurred significantly more often in the female cohort then in the male cohort (f: 69, m: 51) (Table 6) (*P= 0.008*). Minor complications are defined as bleeding, which doesn't need any intervention, first and second-degree AV block or a new bundle branch block. Bleeding, which doesn't need any intervention, was found more often in the female cohort (3.1%) than in the male cohort (1,3%, *P=0.29*). Moderate complications rates were also higher among women (f:5,5%, m:3,4% *P=0.14*) with most of the women developing a pericardial effusion (f: 2,5%, m:1,1% P=0.12) or an arteriovenous fistula (f: 1,8%, m:1,3% *P=0.61*). Major non-fatal complications like stroke, myocardial infarct, and major bleeding had a higher incidence rate in female cohort as well (f: 3.1%, m: 1,3% *P=<0.074*). A clear significance between female and male cohort was found in the development of a major bleeding which needed the intervention of the physician (f: 2,4%, m: 0,7% *P=<0.037*). There was no significant difference regarding secondary arrhythmia until the discharge from the hospital (f: 8,1%, m:7,0% *P=0.51*). The overall hospitalization was significantly longer in female patients than in male patients (f: 5 days, m: 4 days *P<0.001*).

Table 6 Complications in hospital early after catheter ablation

	TOTAL	**FEMALE**	**MALE**	***P- Value ****
Minor Complication	3.9 % (34/876)	4.7 % (19/401)	3.2 % (15/475)	0.290
Moderate Complication	4.4 % (38/873)	5.5 % (22/398)	3.4 % (16/475)	0.140
Major complication	2.1 % (21/994)	3.1 % (14/454)	1.3 % (7/540)	0.074

Data are presented as percentages (%). In parenthesis, data are presented as absolute numbers
NS= Not significant: P > 0.05
*Pearson Chi^2 Test or Mann-Whitney-Wilcoxon Test. All significant P values are in bolt letters.

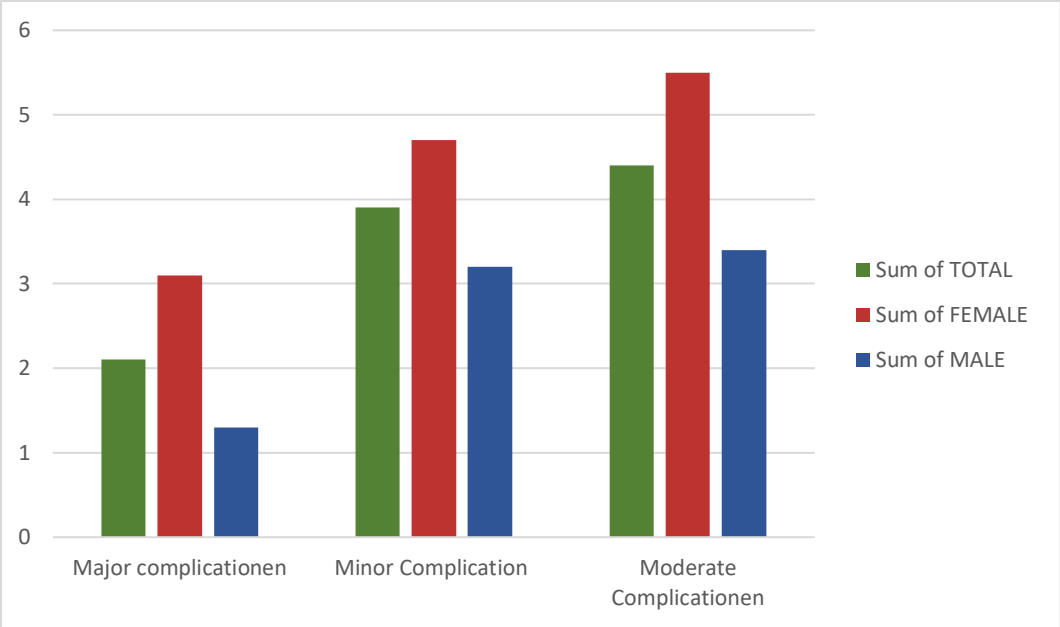


Figure 12 Complications in hospital early after catheter ablation

Drug therapy at the time of release was different between women and men (Table 7). Most patients received beta blockers as a therapy (f: 72.7%, m: 71.5%). More than 50% of the patients did not receive an antiarrhythmic therapy. Digitalis was also more prescribed to men (f:8.1%, m:8.3% *P=0.92*). Diuretics were more prescribed to women (f:43.0%, m:36.1% *P=0.028*). Oral anticoagulation therapy was less often given to women (Macumar f: 87.7%, ASS: f: 10.4%, Clopidogrel f: 2.9%) than to men (Macumar m: 91.1% Marcumar: *P= 0.094*, ASS: m: 11,3 %, ASS *P=0.014*, Clopidogrel m: 5.7%, *P=0.028*).

Table 7 Drug therapy at discharge

	TOTAL	**FEMALE**	**MALE**	***P- Value ****
Released alive	994 (100.0 %)	454 (45.7 %)	540 (54.3 %)	NS
No therapy	0.8 % (8/994)	0.7 % (3/454)	0.9 % (5/540)	0.640
Betablocker	72.0 % (716/994)	72.7 % (330/454)	71.5 % (386/540)	0.670
Antiarrhythmic therapy I/III/IV	48.5 % (482/994)	49.3 % (224/454)	47.8 % (258/540)	0.620
No Antiarrhythmic therapy	51.5 % (512/994)	50.7 % (230/454)	52.2 % (282/540)	0.620
Antiarrhythmic class I	21.0 % (209/994)	21.8 % (99/454)	20.4 % (110/540)	0.580
Antiarrhythmic class III	26.1 % (259/994)	24.7 % (112/454)	27.2 % (147/540)	0.360
Antiarrhythmic class I/III	46.2 % (459/994)	45.8 % (208/454)	46.5 % (251/540)	0.830
Antiarrhythmic class IV	3.2 % (32/994)	4.2 % (19/454)	2.4 % (13/540)	0.110
Digitalis	8.2 % (82/994)	8.1 % (37/454)	8.3 % (45/540)	0.920
Diuretics	39.2 % (390/994)	43.0 % (195/454)	36.1 % (195/540)	**0.028**
Statin	36.8 % (366/994)	32.6 % (148/454)	40.4 % (218/540)	**0.011**
ACE-Hemmer/ARB	57.8 % (575/994)	59.9 % (272/454)	56.1 % (303/540)	0.230
ASS	10.9 % (108/994)	10.4 % (47/454)	11.3 % (61/540)	0.630
Clopidogrel	4.4 % (44/994)	2.9 % (13/454)	5.7 % (31/540)	**0.028**
Marcumar	89.6 % (890/993)	87.9 % (398/453)	91.1 % (492/540)	0.094

Data are presented as percentages (%). In parenthesis, data are presented as absolute numbers
NS= Not significant: $P > 0.05$
*Pearson Chi^2 Test or Mann-Whitney-Wilcoxon Test. All significant P values are in bolt letters.

4.4. Gender differences in the one year follow up

The follow-up was performed by telephone by the Institut für Herzinfarkt Forschung (IHF) in Ludwighafen one year after the ablation. In total 983 patients were reached (f:448, m:535). During the year 15 women and 18 men died. The exact cause of death was not found out.

Most patients in both gender groups notified either a reduction of symptoms or no symptoms at all (f: 86%, m:79,7% *P=0.014*). There was no significant difference between female and male patients who reported an increase in worsening of the symptoms (f: 5%, m:

2,6% *P=0.063*). At the follow up more women described symptoms like angina pectoris (f:21.8%, m:11.7%, *P=0.003*) and had more severe physical limitations, classified with NYHA (NYHA II+ f:58.6%, m: 40.6%, *P= 0.001*). This presents a significant gender difference. Women also had significantly higher incidence in documented AF recurrency than men (f:46,2%, m:39,5%, *P=0.038*).

Table 8 Symptoms One year follow up

	TOTAL	**FEMALE**	**MALE**	***P- Value ****
No symptoms	17.5 % (156/893)	14.0 % (56/400)	20.3 % (100/493)	**0.014**
Symptoms	82.5 % (737/893)	86.0 % (344/400)	79.7 % (393/493)	**0.014**
Less symptoms	61.0 % (545/893)	60.3 % (241/400)	61.7 % (304/493)	NS
Unchanged symptoms	17.8 % (159/893)	20.8 % (83/400)	15.4 % (76/493)	NS
Worse symptoms	3.7 % (33/893)	5.0 % (20/400)	2.6 % (13/493)	0.063

Data are presented as percentages (%). In parenthesis, data is presented as absolute numbers (Patent with comorbidity vs sample size) NS= Not significant: P > 0.05
*Pearson Chi^2 Test or Mann-Whitney-Wilcoxon Test. All significant P values are in bolt letters.

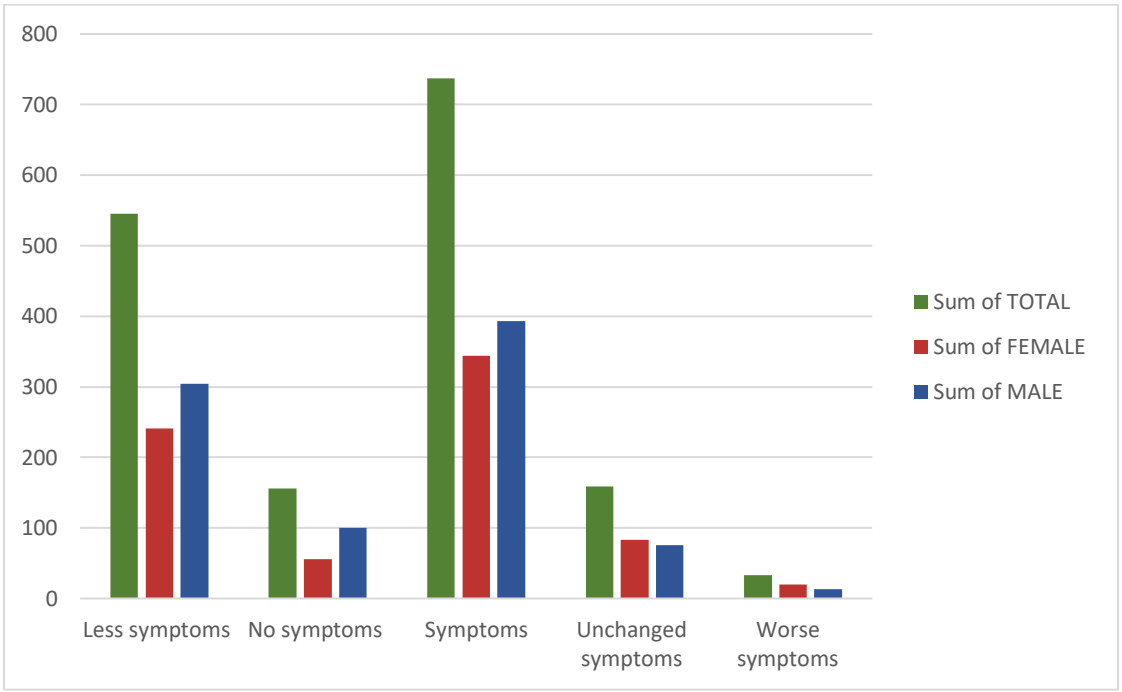


Figure 13 Symptoms One year follow up

Table 9 New York Heart Association Classification One year Follow up

	TOTAL	**FEMALE**	**MALE**	***P- Value****
NYHA 1	50.0 % (399/798)	40.5 % (147/363)	57-9 % (252/435)	NS
NYHA 2	31.0 % (247/798)	31.7 % (115/363)	30.3 % (132/435)	NS
NYHA 3	13.3 % (106/798)	19.6 % (71/363)	8.0 % (35/435)	NS
NYHA 4	3.4 % (27/798)	6.1 % (22/363)	1.1 % (5/435)	NS
NYHA 2+	48.8 % (380/779)	58.6 % (208/355)	40.6 % (172/424)	**<0,001**

Data are presented as percentages (%). In parenthesis, data is presented as absolute numbers.
NS= Not significant: P > 0.05
*Pearson Chi^2 Test or Mann-Whitney-Wilcoxon Test. All significant P values are in bolt letters.

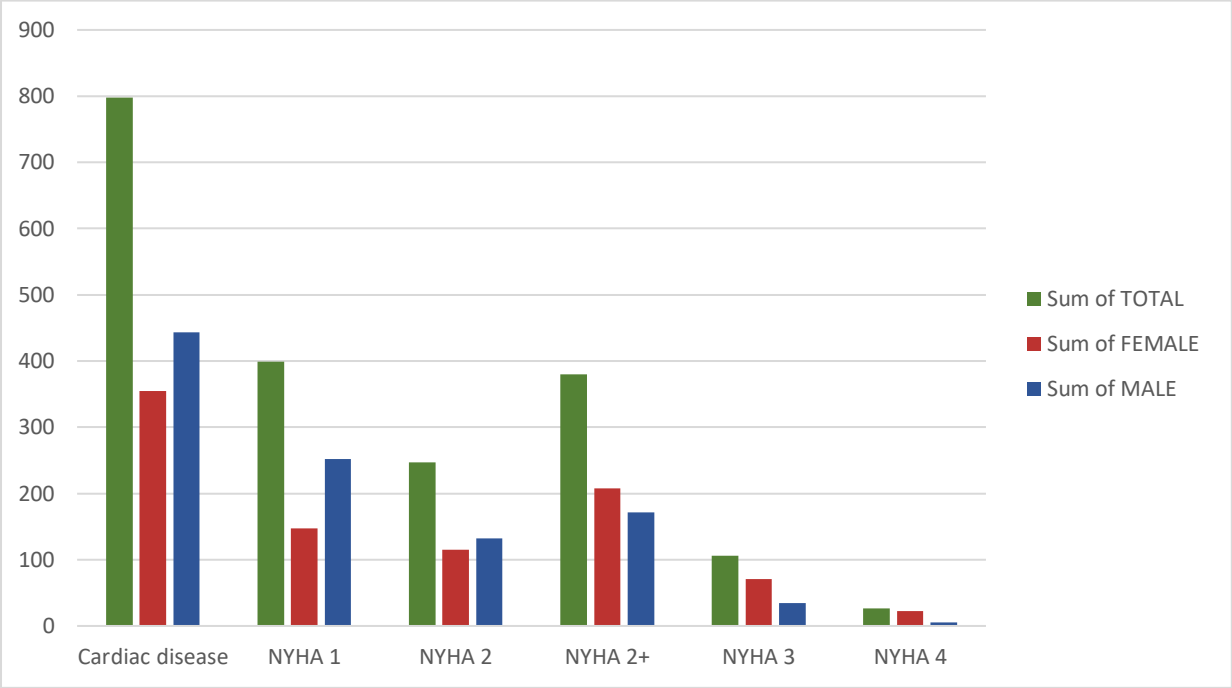


Figure 14 New York Heart Association Classification One year Follow up

Moderate complications rates and major complication were presented in the same manner in female and male patients.

Table 10 Complication One year Follow up N= 950

	TOTAL	FEMALE	MALE	*P- Value**
Moderate Complication	8.9 % (69/779)	9.1 % (32/353)	8.7 % (37/426)	0.850
Major complication	2.9 % (26/906)	3.2 % (13/409)	2.6 % (13/497)	0.610

Data are presented as percentages (%). In parenthesis, data is presented as absolute numbers. NS= Not significant: P > 0.05
*Pearson Chi^2 Test or Mann-Whitney-Wilcoxon Test. All significant P values are in bolt letters.

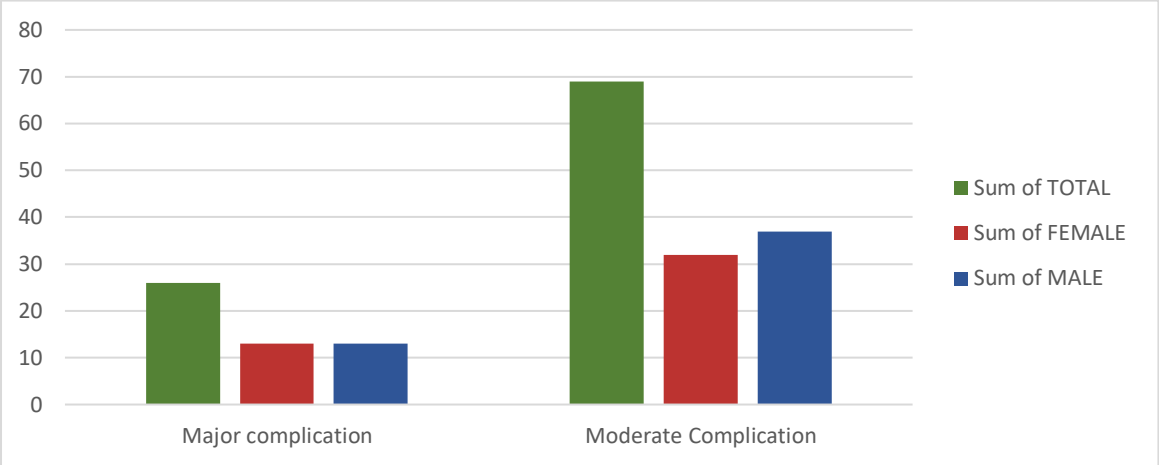


Figure 15 Complication One year Follow up N= 950

In the one year follow up female and male patients showed comorbidities like chronic liver diseases, rhematic diseases, and cancer in a same manner. A significant difference was found in thyroid diseases which were more often diagnosed in female patients (f: 32,4 %, m: 11,6 % *P< 0,001*).

Table 11 Comorbidities One year follow up

	TOTAL	FEMALE	MALE	*P- Value**
Chronic liver disease	3.3 % (12/369)	4.1 % (7/172)	2.5 % (5/197)	0.410
Rheumatic disease	7.8 % (29/370)	8.7 % (15/172)	7.1 % (14/198)	0.560
Thyroid disease	21.4 % (80/374)	32.4 % (57/176)	11.6 % (23/198)	**<0.001**
Cancer	10.9 % (40/368)	10.5 % (18/172)	11.2 % (22/196)	0.82

Data are presented as percentages (%). In parenthesis, data is presented as absolute numbers (Patent with comorbidity vs sample size) NS= Not significant: P > 0.05
*Pearson Chi^2 Test or Mann-Whitney-Wilcoxon Test. All significant P values are in bolt letters.

Men had received a secondary catheter ablation slightly more frequently (f:19.7%, m:20.7% *P=0.63*) whereas women had a significantly higher rate of SM/ICD/CRT implantation (f: 7.4%, m:2.9% *P=0.002*). The overall rehospitalization rate was roundabout fifty percent of the cohort and slightly more pronounced in women than in men (f: 54.2%, m: 48.2% *P=0.10*). The rehospitalization in the one year follow up was mostly due to cardiovascular causes (f: 70.3%%, m: 73.9 *P=0.40*).

Table 12 Implantation: Pacemaker/ Implantable cardioverter defibrillator (ICD)/ Cardio resynchronization therapy (CRT) One year Follow up

	TOTAL	**FEMALE**	**MALE**	***P- Value****
Hx of Impl. Pacemaker/ICD/CRT	4.9 % (46/932)	7.4 % (31/421)	2.9 % (15/511)	**0.002**
Hx of Impl. Pacemaker	4.4 % (41/932)	6.9 % (29/421)	2.3 % (12/511)	**<0,001**
Hx of Impl. ICD	0.5 % (5/932)	0.5 % (2/421)	0.6 % (3/511)	0.820
Hx of Impl. CRT	0.0 % (0/932)	0.0 % (0/421)	0.0 % (0/511)	NS

Data are presented as percentages (%). In parenthesis, data is presented as absolute numbers
NS= Not significant: P > 0.05
*Pearson Chi^2 Test or Mann-Whitney-Wilcoxon Test. All significant P values are in bolt letters.

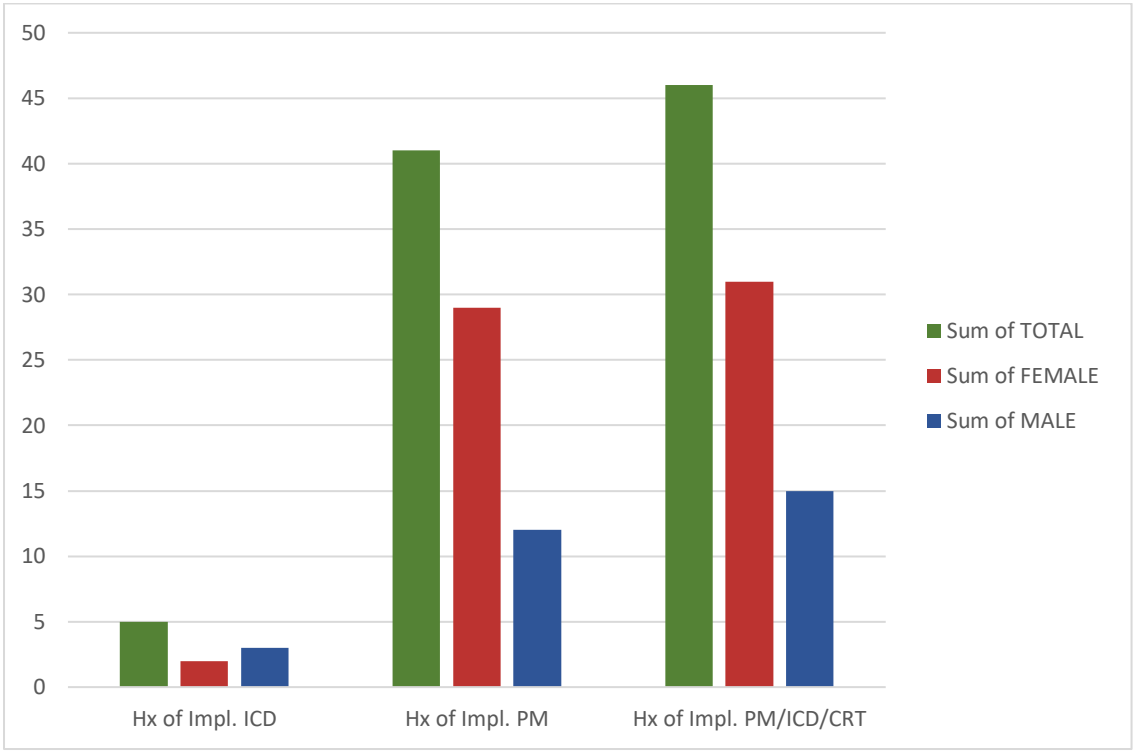


Figure 16 Implantation: Pacemaker (PM)/ Implantable cardioverter defibrillator (ICD)/ Cardio resynchronization therapy (CRT) One year Follow up

Most patients received beta blockers as a therapy (f: 78.9%, m: 72.7% *P=0.034*). More than 60% of the patients did not receive an antiarrhythmic therapy. Digitalis was more prescribed to women (f:10.4%, m:6.1% *P=0.018*) as well as diuretics (f:49.5%, m:34% *P<0.001*). Oral anticoagulation therapy was significantly given more frequently to women (f: 57.7%) than to men (m: 49.5%, *P=0.014*).

Table 13 Drug therapy One year follow up

	TOTAL	**FEMALE**	**MALE**	***P- Value****
Betablocker	75.5 % (674/893)	78.9 % (317/402)	72.7 % (357/491)	**0.034**
Antiarrhythmic therapy I/III/IV	33.6 % (300/893)	35.3 % (142/402)	32.2 % (158/491)	0.320
No Antiarrhythmic therapy	66.4 % (593/893)	64.7 % (260/402)	67.8 % (333/491)	0.320
Antiarrhythmic class I	12.8 % (114/893)	13.7 % (55/402)	12.0 % (59/491)	0.460
Antiarrhythmic class III	18.0 % (161/893)	18.7 % (75/402)	17.5 % (86/491)	0.660
Antiarrhythmic class I/III	30.3 % (271/893)	32.1 % (129/402)	28.9 % (142/491)	0.310
Antiarrhythmic class IV	3.9 % (35/893)	4.2 % (17/402)	3.7 % (18/491)	0.670
Digitalis	8.1 % (72/893)	10.4 % (42/402)	6.1 % (30/491)	**0.018**
Diuretics	41.0 % (366/893)	49.5 % (199/402)	34.0 % (167/491)	**<0.001**
Statin	35.8 % (320/893)	34.6 % (139/402)	36.9 % (181/491)	0.480
ACE-blocker /ARB	64.4 % (575/893)	67.2 % (270/402)	62.1 % (305/491)	0.120
ASS	28.2 % (252/893)	24.6 % (99/402)	31.2 % (153/491)	**0.031**
Clopidogrel	3.7 % (33/893)	2.7 % (11/402)	4.5 % (22/491)	0.170
Oral anticoagulation)	53.2 % (475/893)	57.7 % (232/402)	49.5 % (243/491)	0.014
Heparin (UFH)	0.2 % (2/893)	0.2 % (1/402)	0.2 % (1/491)	0.890
Low molecular weight Heparin (LMWH)	1.0 % (9/893)	1.5 % (6/402)	0.6 % (3/491)	0.190

Data are presented as percentages (%). In parenthesis, data is presented as absolute numbers.
NS= Not significant: P > 0.05
*Pearson Chi^2 Test or Mann-Whitney-Wilcoxon Test. All significant P values are in bolt letters.

5. DISCUSSION

In this study a total of 995 patients received a CA due to AF. Overall female patients represented were older than male patients at the time of CA (Table 1). This seemed to be a general finding as it was stated in several papers (5, 12, 17, 19).

The results of this study showed that elderly female patients had a lower incidence of cardiac comorbidities like coronary artery diseases, prior myocardial infarct, cardiomyopathies, and a reduced left ventricular function compared to male patients (Table 2). Piccini JP *et al.* also stated in their study that men were diagnosed more with coronary heart diseases like a previous myocardial infraction (12). The results of the present study characterized that the comorbidities like arterial hypertension, diabetes mellitus and stroke were more common in elderly female patients, but these results were not significant (Table 2). A lot of studies declared that female patients are diagnosed more frequently with comorbidities like atrial hypertension, valve defects, diastolic heart failure and had a history of thyroid dysfunction and diabetes mellitus (5-8, 12, 13, 17, 21). Our results showed that female patients reported a higher appearance of thyroid diseases in the follow up (Table 11).

Studies showed that female patients with atrial fibrillation often developed more severe symptoms and were associated with a worse prognosis (5, 20, 21). Nearly all patients in this study described palpitations occurring at minimum at least once a month. Elderly female patients noticed symptoms like presyncope more often than elderly men whereas men experienced more frequent syncopes. But these gender differences were not significant in this study (Table 5). Other published papers represented more pronounced symptoms in females like a higher ventricular response rate, longer episode of duration or more severe reduction of quality of life (5, 8, 22).

The CHA_2DS_2-VASc Score is the method to predict thromboembolic events. Due to the CHA_2DS_2-VASc Score female patients and patients aged between 65-75 have already increased risks for such events (5, 12, 30, 31). This tendency was also seen in our study. The CHA_2DS_2-VASc Score in elderly female patients was significantly higher than in elderly male patients. A lot of studies demonstrated a correlation between AF and stroke in female patients (13, 26). These studies described permanent damage with a worse long-term outcome after stroke (5). Our results showed a gender difference. Seven female patients out of eighty-four experienced a stroke before the procedure whereas only three male patients out of seventy-five had a stroke. These results were not significant, this could be because of the low response rate of the sample size (Table 2). The pathology behind a stroke is a clot formation in the left appendage in the

LA (2, 9). Reasons for the increased incidence of stroke in female patients could be due to female sex hormones, which may play a prothrombotic role via effects on platelet and endothelial function. It could also depend on the higher rate of atrial fibrosis in AF, this contributes to the abnormal clotting in the LA.

All patients receiving a catheter ablation in our study had a history of AF. Piccini JP *et al.* state that women in an SA rhythm were more frequently ablated and underwent more AV Node ablations (12). In this study the catheter ablation was also performed mainly during SA rhythm but most of the patients received circumferential PV-ablation. In general, the procedure time with radiofrequency therapy was shorter in elderly females than in elderly males, one explanation could be the smaller LA than in men. (5, 28). Our results confirmed this statement that the procedure-time is significantly lower in the female cohort.

Most studies show that women have a significantly reduced success rate than men (5-7). The reason for those findings could be that female patients are older at the time of CA, that they have increased CHA_2DS_2-VASc scores and higher comorbidities. Women also showed higher rates of longstanding persistent atrial fibrillation and failed more antiarrhythmic agents, and they were referred for ablation in a later clinical course (5, 19, 22 29). This study showed no significant difference in the success rate. The procedure results were successful in 96.1% of the cohort. A partial success, in which not all the electrophysiological morphologies where ablated, was achieved in 2.2% of the female cohort and in 2.4% of the male cohort. No success after the catheter ablation was seen in eleven women and in five men.

In our study the periprocedural and postprocedural mortality was very low in both cohorts with only one female dying from an unknown cardiovascular cause. The overall hospitalization in this study was significantly longer in elderly female patients than in elderly male patients. A lot of studies mirrored that the complication rate in female patients is higher than in male patients, but the results were not interiorly uniform (5, 6, 19, 21-23, 29). In the study from Kennedy *et al.* it was stated that elderly patients had a reduce apparency of major complications like thromboembolic events and pericardial effusions, compared to younger patients (32). Other studies demonstrate that in particular hospital complications were significantly higher in the female sex (19, 21, 22, 29). Our results confirmed that the overall non-fatal complications occurred significantly more often in the elderly female cohort then in the elderly male cohort (Table 6). In other studies, a significantly higher incidence of cardiac perforations with a cardiac tamponade, access-site bleeding and hematoma were found in

women (22, 5-7, 19, 21, 29). In this study minor complications were defined as bleeding, which did not need any intervention, first and second-degree AV block or a new bundle branch block. Bleeding, which did not need any intervention, were found more often in the female cohort than in the male cohort but did not show a significant result. Moderate complication rates were also higher among elderly women, but also did not show a significant result. Most of the elderly women developed a pericardial effusion or an arteriovenous fistula. Major non-fatal complications like stroke, myocardial infarct, and major bleeding had a higher incidence in female cohort as well, but the difference to the male cohort was not significant (Table 6). A clear significance between the elderly female and elderly male cohorts was found in the development of a major bleeding which needed the intervention of the physician. There was no significant difference regarding secondary arrhythmia until the discharge from the hospital. These findings could be explained by anatomical differences in the thinner wall of the LA in women or due to the increased age of the women (5-7, 17, 19, 21, 22). Some studies showed that elderly women with AF are less likely to be prescribed anticoagulation therapy than elderly men, however this study expressed different results (7, 12-14, 23). The oral anticoagulation therapy was given significantly more frequently to women than to men at the time of discharge (Table 7).

In this study most patients in both gender groups notified either a reduction of symptoms or no symptoms at all. There was no significant difference between female and male patients who reported an increase in worsening of the symptoms (Table 8). Studies including a follow up after the CA showed that female patients had a higher risk of AF recurrency than male patients which was also confirmed in this study (17, 21, 22). Female patients had a significantly higher incidence in recurrency of AF than in male patients. Women described more severe limitations in physical capacity as classified by NYHA states and more often experienced angina pectoris (22). These results were also seen in the follow up in this study. Women described more frequent symptoms such as angina pectoris and had more severe physical limitations, classified with NYHA, which presented a significant gender difference (Table 8, 9).

In previous studies most patients received beta-blockers, but a slightly higher prescription rate was seen in female patients (17, 22). Women also received more digitalis as well as anticoagulation therapy, supported by similar results in our study (22). In our studies most of the elderly patients received beta blocker as a therapy. More than 60% of the patients did not receive an antiarrhythmic therapy. Digitalis was prescribed more to women as well as

diuretics (Table 13). Oral anticoagulation therapy was also given significantly more frequently to women than to men.

Overall elderly patients were less likely to undergo a repeat ablation (32). In generally women were less likely to receive a cardioversion or repeat ablation procedure but more pacemaker implantations were required by women (17, 22). This study also states a significant increase in pacemaker implantation in elderly women (Table 12), but an increased tendency in repeated CA ablation was seen in elderly men, which was controversial as elderly women had a significantly higher incidence in AF recurrency.

Studies show that the overall hospitalization was higher in women compared to men especially the re-hospitalization due to AF (17, 22). In this study the overall rehospitalization rate was roundabout fifty percent of the cohort and slightly more pronounced in women than in men but the result was not significantly.

This study carried common strengths of a large registry analysis. The German Ablation Registry is one of the largest worldwide. In the years 2007-2010 patient data was collected in patients receiving CA with AF. In sum a sample size of 3652 patients was reached (22). From this large data pool, a subgroup of 995 patients over the age of 70 was selected. In most studies had an underrepresentation of women in ablation trials, but in this study the group of female patients nearly had the same sample size as men. The sex-related differences in comorbidities represented in the cohort were common in everyday practice and indicated that this study reflects a real-life patient population.

A limitation of this study is that for this particular patient group the sample size was relatively small, and a bigger sample size could have influence the study results. The groups displayed differences in parameters, but the more detailed differences between groups were not statistically significant. This study failed to identify the correlation between comorbidities and the complication rate after CA. This would allow for a better comparison of the complications due to CA and comorbidities or solely due to CA. An underrepresentation of procedural parameter could not be excluded as the data collection in the centers was voluntary. Certain parameters were not registered for all patients owing to changes in the study protocol, including comorbidities like kidney insufficiency, hypertension, stroke etc. Some baseline parameters like medications before CA and Body Mass Index (BMI), the time of first AF diagnosis, the left atrial dimensions were not documented and therefore could not be included in the present study.

The follow-up was performed by telephone one year after the initial ablation, which is also a strength of this study. In most studies follow ups were performed by a written questionnaire or by personal meeting, which were often answered in less detail. During the call the patients were asked if they experienced any adverse effects or if they noticed symptoms and if they required another catheter ablation. The result of this study showed a significant sex-related difference in overall non-fatal complication early after CA and in the follow up women described more often symptoms like angina pectoris and had more severe physical limitations, classified with NYHA.

Unfortunately, long-term follow-up was limited to patients until 2010. In the last decade physicians collected more experiences and CA received more technical advances. This may have led to a reduction in complications and an improvement in procedural success.

Women are significantly underrepresented in clinical trials and studies, which makes interpretation of the data and understanding the true risk and benefit of different management and treatment strategies difficult. For a better understanding further studies would be needed.

6. CONCLUSION

- According to these results, we concluded CA of AF in elderly patients was associated with a distinct sex-related outcome and complication profile.
- This study conclusively showed sex-related differences in elderly patients in the one year follow up.
- The one-year follow up of this study clarified that there was an increased recurrency of AF in elderly women than in elderly men.
- The differences in the clinical management with antiarrhythmic therapy and anticoagulation therapy after the CA could also determine the outcome characteristics.

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10. SUMMARY

BACKGROUND Atrial fibrillation (AF) is defined as a rapid, irregular heart rate, which makes it impossible for the heart to pump the blood adequately in the arteries. In women, AF is associated with more severe symptoms and worse prognosis. Catheter ablation is often described as the cure of AF, compared with antiarrhythmic therapy, which is just controlling the AF.

OBJECTIVE We sought to assess sex-related differences in complications after catheter ablation in elderly patients with atrial fibrillation

METHODS A total of 995 patients (female (f): 455(45.7%), male (m): 540 (54,3%)) over 70 years receiving a cardiac ablation after atrial fibrillation from January 2007- January 2010 with a one year follow-up were gathered from the German Ablation Registry and were compared between male and female patients.

RESULTS The median age for both sex is 73 years. 125 (27.5%) females and 122 (22.6%) males are older than 75 years. Elderly male patients had a higher incidence of cardiac comorbidities (f: 48.4%, m: 58.9%, P=<0.001). Other comorbidities had a higher frequency in elderly female patients, but these results were not significant. Nearly all patients (female: 98,5%, male: 98,1% P= 0.7) described palpitations occurring at minimum once a month. In female patients the CHA_2DS_2- VASc-Score is significantly higher than in men (P=<0.001) but overall, the procedure-time was lower in the female cohort (1800 sec. female, 2340 sec. male, P=<0,025). There was no significant difference in the success rate (female 95.4%, male 96.7% P= 0.30). Overall non-fatal complications occurred more often in the female cohort then in the male cohort, and mainly driven by major bleeding events (f: 2,4%, m: 0,7% P=<0.037). At the follow up most patients in both gender groups notified either a reduction of symptoms or no symptoms at all (f: 86%, m:79,7% P=0.014). There was no significant difference between female and male patients who reported an increase in worsening of the symptoms (f: 5%, m: 2,6% P=0.063). Women also had a significantly higher incidence rate in documented AF recurrency than men (f:46,2%, m:39,5%, P=0.038) and had more severe physical limitations, classified with NYHA (NYHA II+ f:58.6%, m: 40.6%, P= 0.001). Moderate complications rates and major complication were presented in the same manner in elderly female and elderly male patients. Most patients received beta blocker as a therapy, but women received oral medication for rhythm and rate control more frequently.

CONCLUSION Catheter ablation of AF in elderly patients was associated with a connection between gender differences and the complications rates. This study clarified that there is an increased recurrency of AF in elderly women than in elderly men in the one-year follow up.

11. CROATIAN SUMMARY

NASLOV: SPOLNE RAZLIKE U VEZI KOMPLIKACIJA U STARIJIH BOLESNIKA S ABLACIJOM ATRIJSKE FRIBRILACIJE

POZADINA: Fibrilacija atrija (AF) definira se kao brz, nepravilan ritam otkucaja srca, koji onemogućuje srcu da adekvatno pumpa krv u arterije. U žena, AF povezujemo s težim simptomima i lošijom prognozom. Kateterska ablacija se često opisuje kao lijek za AF, u usporedbi s antiaritmičkom terapijom, koja samo kontrolira AF.

CILJ: Pokušali smo procijeniti spolne razlike u komplikacijama nakon kateterske ablacije u starijih bolesnika s fibrilacijom atrija

METODE: U Ukupno 995 pacijenata (žene (ž): 455 (45,7%), muškarci (m): 540 (54,3%)) tijekom 70 godina primijenjena je ablacija srca nakon fibrilacije atrija od siječnja 2007. do siječnja 2010. uz jednogodišnje praćenje, prikupljeno je iz njemačkog registra ablacije i uspoređeno između muških i ženskih pacijenata.

REZULTATI: Prosječna dob za oba spola je 73 godine. 125 (27,5%) žena i 122 (22,6%) muškaraca starije je od 75 godina. Stariji muški bolesnici imali su veću incidenciju srčanih komorbiditeta (f: 48,4%, m: 58,9%, P=<0,001). Ostali komorbiditeti bili su češći u starijih bolesnica, ali ti rezultati nisu bili značajni. Gotovo svi bolesnici (žene: 98,5%, muškarci: 98,1% P= 0,7) opisali su palpitacije koje se javljaju najmanje jednom mjesečno. U pacijentica CHA2DS2-VASc-score je značajno viši nego u muškaraca (P=<0,001), ali ukupno, vrijeme postupka bilo je kraće u ženskoj kohorti (1800 sekundi žena, 2340 sekundi muškarac, P=<0,025) . Nije bilo značajne razlike u stopi uspješnosti (žene 95,4%, muškarci 96,7% P= 0,30). Ukupne nefatalne komplikacije češće su se javljale u ženskoj nego u muškoj skupini, a uglavnom su potaknute velikim krvarenjima (f: 2,4%, m: 0,7% P=<0,037). Tijekom praćenja većina bolesnika u oba spola zabilježila je smanjenje simptoma ili nepostojanje simptoma (f: 86%, m:79,7% P=0,014). Nije bilo značajne razlike između žena i muškaraca koji su prijavili povećanje pogoršanja simptoma (f: 5%, m: 2,6% P=0,063). Žene su također imale značajno višu stopu incidencije kod dokumentiranog ponavljanja AF od muškaraca (f:46,2%, m:39,5%, P=0,038) i imale su ozbiljnija fizička ograničenja, klasificirana s NYHA (NYHA II+ f:58,6% , m: 40,6%, P = 0,001). Stope umjerenih komplikacija i velike komplikacije prikazane su na isti način u starijih žena i starijih muškaraca. Većina pacijenata primala je beta blokator kao terapiju, ali žene su češće primale oralne lijekove za kontrolu ritma i brzine.

ZAKLJUČAK: Kateterska ablacija AF povezana je s korelacijom između spolnih razlika i komplikacija u starijih bolesnika. Ova studija je pojasnila da postoji povećana stopa recidiva AF u starijih žena nego u starijih muškaraca tijekom jednogodišnjeg praćenja

12. CURRICULUM VITA

EDUCATION

10/2016- today	Medicine; University of Split (Croatia) and Medical School REGIOMED
04/2013 – 03/2016	Bachelor of Art in Education (Grade 1,3) . Bachelor Thesis: „Mädchenbildung in Indien am Fallbeispiel Heartkids“ (Grade1,0) . Minor subject Psychology
09/2010– 06/2012	High-school Diploma (Grade 2,3) | Dietrich-Bonhoeffer-Gymnasium Weinheim| BW
08/2009-07/2010	Year aboard: Boarding School Kingham Hill School England, Oxfortshire, Kingham
09/2004-07/2009	Heinrich Sigmund Gymnasium |Schriesheim |BW

WORK EXPIRENCE

01-02/2022	Clinical Rotation | University Hospital Heidelberg | Gynecology |Cardiology |Traumatology
09/2021	Clinical Rotation | University Hospital Heidelberg | Heart surgery
03/2016-06/ 2016	Education to a paramedic | Franz Anton Mai Schule | Arbeiter Samariter Bund |Mannheim |
1/2016- 2/2016	St. Hedwig Klinik | Mannheim | Internship
07/2015- 9/2015	Gesundheitszentren Rhein-Neckar gGmbH | Weinheim |grn.de Internship
02/2015 – 03/2015	Heartkids e.V. | Indien, Thiruvannamailai | heartkids.de Voluntary work as a teacher and educational assistant
03/2014 – 02/2015	AWO Kindertagesstätte Hausen | Frankfurt am Main | awo-frankfurt.com | Educational Assistant
04/2013 –03/2014	Alte Oper in Frankfurt am Main | Hostess |alteoper.de