Diploma Thesis

Catheter ablation in patients with atrial fibrillation and reduced ejection fraction

submitted by

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Statutory Declaration

I hereby declare that I have written this thesis by my own and without any assistance from third parties, have not used any sources other than those specified in the thesis itself and have clearly attributed any used concepts or quotations applicable to these sources.

Graz, 22 August 2020 *Darko Trajanoski eh*

Acknowledgement

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Abstract

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in adults, (1) with catheter ablation being an established second-line therapy. (2) AF frequently occurs in patients with heart failure (HF) and leads to a worse prognosis. (3) Conversely, HF with reduced ejection fraction (HFrEF) has been proposed as a predictor of poorer outcome in catheter ablation procedures. (4, 5) Therefore, this thesis aimed to investigate the long-term outcome of patients with HFrEF undergoing AF catheter ablation.

Methods

Patients undergoing AF catheter ablation at the University Hospital of Graz were assigned to one of two groups according to their left ventricular systolic function (LVEF). Relevant patient data was collected retrospectively in a registry from 2011 until 2018. Success was defined as AF and atrial tachycardia free survival during follow up. Rhythm was monitored at 3- and 12-months following the procedure by means of 24-hour Holter ECG monitoring.

Results

274 patients were included in the analysis. 243 patients had normal left ventricular function (nEF, 64±5%), while 31 patients had reduced systolic function (rEF, 49±10%). Baseline characteristics were largely comparable, though atrial enlargement was more frequent in rEF patients (48 vs. 25%, P=0.005).

Single procedure success rate was 59% in nEF patients and 67% in rEF patients (log rank test: P=0.203) after a follow-up duration of 340 (122, 555) vs. 192 (107, 452) days (P=0.12). Complication rate was low in both study cohorts. Repeat ablations were performed in 19 vs. 23% of patients (P=0.17).

Discussion

There was no significant difference in outcome and complication rate between the nEF and rEF group. Therefore, it can be concluded that catheter ablation is reasonable and safe for the treatment of AF in patients with HFrEF.

Zusammenfassung

Einführung

Katheter-Ablation ist die empfohlene Zweitlinientherapie bei Patientinnen und Patienten mit Vorhofflimmern (VHFA), welches die häufigste Rhythmusstörung bei Erwachsenen darstellt. (1, 2) Es wurde gezeigt, dass VHFA mit begleitender Herzinsuffizienz zu einer schlechteren Prognose führt. (3) Im Gegenzug dazu ist Herzinsuffizienz mit reduzierter Auswurfsfraktion (HFrEF) mit einer schlechteren Erfolgsrate nach Katheter-Ablation vergesellschaftet. (4, 5) Ziel dieser Diplomarbeit war es, die Langzeit-Erfolgsrate von Katheter-Ablation bei Patientinnen und Patienten mit VHFA und HFrEF zu untersuchen.

Methoden

Patientinnen und Patienten, die sich zwischen 2011 und 2018 einer Katheter-Ablation am LKH Universitätsklinikum Graz unterzogen haben, wurden entsprechend ihrer links-ventrikulären Funktion (LVEF) in zwei Studienkohorten unterteilt. Hierzu wurden relevante gesundheitliche Daten in einem Register retrospektiv gesammelt. Der Erfolg einer Katheter-Ablation wurde als Arrhythmie-freies Überleben während der Follow-Up-Phase definiert, welches 3 und 12 Monate nach der Prozedur mittels 24-Stunden Holter EKG überprüft wurde.

Ergebnisse

274 Patientinnen und Patienten wurden in die Studie einbezogen, von diesen hatten 243 normale LVEF (nEF, 64±5%) und 31 eine reduzierte LVEF (rEF, 49±10%). Die Baseline-Charakteristika waren vergleichbar zwischen den Gruppen, jedoch zeigte sich bei der rEF-Gruppe ein höherer Anteil an Personen mit atrialer Dilatation (48 vs. 25%, p=0.005). Die Erfolgsrate nach einer einzelnen Ablationsprozedur betrug 59% in der nEF und 67% in der rEF Kohorte (log-rank test: P=0.203) nach einer Follow-Up Dauer von 340 (122, 555) verglichen mit 192 (107, 452) Tagen (P=0.12). Insgesamt gab es wenig Komplikationen in beiden Gruppen. Die Ablationsprozedur wurde in 19% verglichen mit 23% der Patientinnen und Patienten wiederholt (P=0.17).

Diskussion

Hinsichtlich der Erfolgs- und Komplikationsrate wurde kein signifikanter Unterschied zwischen der nEF und rEF Kohorte festgestellt. Folglich stellt die Katheter-Ablation eine effektive und sichere Therapie von VHFA bei Patientinnen und Patienten mit HFrEF dar.

Glossary

AF	atrial fibrillation
HF	heart failure
CHF	congestive heart failure
bpm	beats per minute
AV	atrioventricular
ECG	electrocardiogram
AFL	atrial flutter
AT	atrial tachycardia
ACS	acute coronary syndrome
hs-CRP	high-sensitivity C-reactive protein
BNP	brain natriuretic peptide
CAD	coronary artery disease
ESC	European Society of Cardiology
AP	action potential(s)
ACE	angiotensin converting enzyme
LA	left atrium
LAA	left atrial appendage
OAC	oral anticoagulants
NOAC	novel oral anticoagulants
VKA	vitamin K antagonists
AAD	antiarrhythmic drug
LVEF	left-ventricular ejection fraction
RF	radiofrequency energy
PV	pulmonary veins
PVI	pulmonary vein isolation
CTI	cavotricuspid isthmus
NYHA	New York Heart Association
TTE	transthoracic echocardiography
TEE	transesophageal echocardiography
ATP	adenosine triphosphate

1 Introduction

The purpose of this thesis and the underlying study is to investigate the effectiveness of catheter ablation in patients with atrial fibrillation (AF) and concomitant heart failure (HF). For this reason, data from patients undergoing catheter ablation of AF at University Hospital Graz was collected and analyzed retrospectively. This section provides an outline of the definition, pathophysiological mechanisms and management of AF in the first part as well as HF in the second part. Furthermore, the third part gives a comparison of both diseases, their interaction and describes the CASTLE-AF trial, (6) which was a major study addressing the given research question prior to this thesis.

1.1 Atrial fibrillation (AF)

1.1.1 Definition

Atrial fibrillation is defined as a tachycardic, irregular arrhythmia originating in the heart atrium, therefore it is classified as a supraventricular tachycardia. The atrium is firing in complete disorder, thereby exceeding frequencies over 300 bpm. Due to the high frequencies and irregular nature of the contractions the mechanical function of the atrium is impaired. The atrioventricular node, if functioning properly, has a filtering function for the high frequencies of the atrium in patients with AF, resulting in lower ventricular frequencies (usually under 150 bpm). Ventricular activity remains irregular though.
AF is characterized by the absence of P-waves in all ECG-leads, instead there are unorganized and rapid waves varying in shape and size. Therefore, in order to diagnose AF an ECG must be performed. (7)

The European Society of Cardiology has defined the following criteria for the diagnosis of AF using an ECG:

- *“Absolutely irregular RR intervals*
- *no discernible, distinct P waves*
- *an episode lasting at least 30 seconds”* (2)

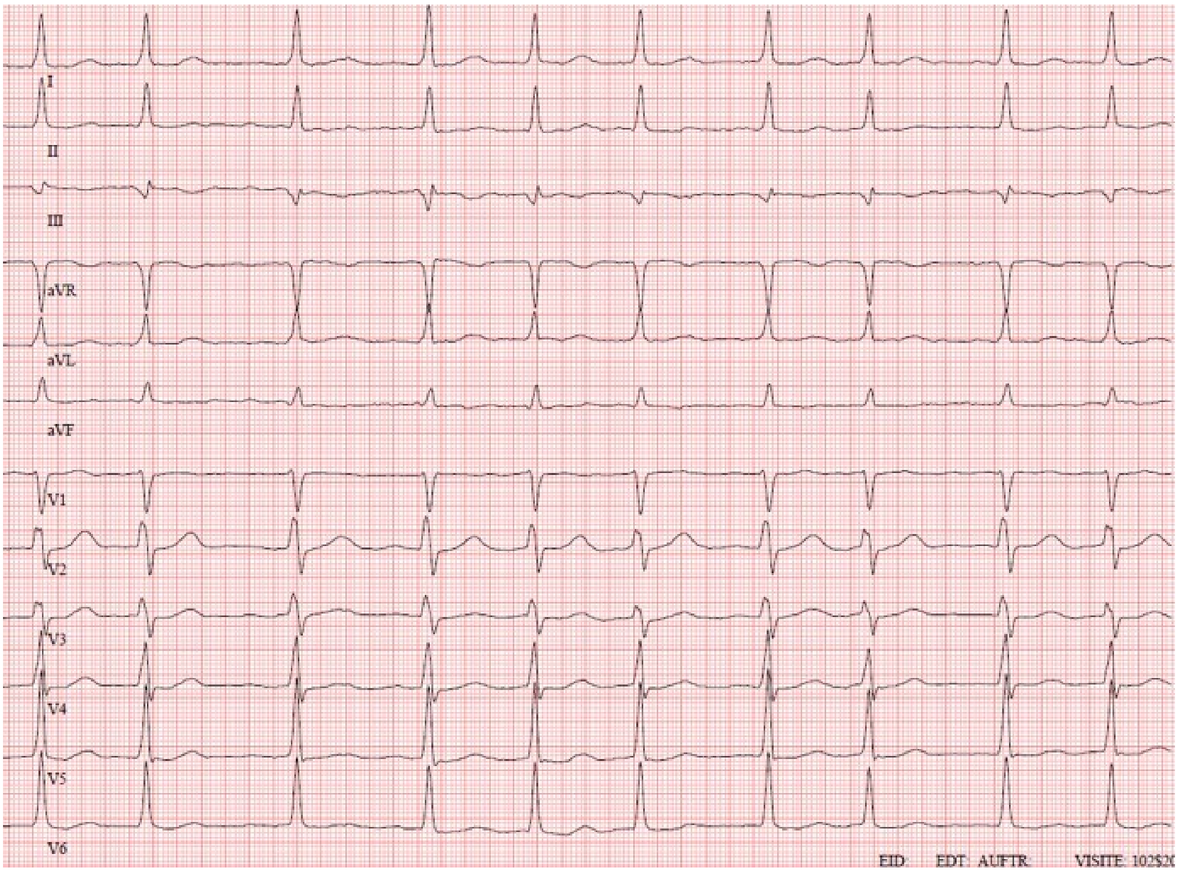

Figure 1: ECG showing atrial fibrillation (AF). By courtesy of Dr. med. univ. Martin Manninger-Wünscher.

Clinical Classification

AF usually occurs in the form of self-limiting episodes; these episodes range from a duration of less than a minute to several hours and vary in the frequency of occurrence from once per year to several times a day (= paroxysmal AF). The first detected episode is described as "initial event". Sometimes an AF episode can last more than a week (= persistent AF), more than a year (= long standing persistent) and/or require pharmacological or electrical intervention for termination. In the most severe cases an AF episode can become resistant to cardioversion or relapse shortly after. If the patient and physician agree on ceasing rhythm control therapy in the process, the AF is described as "permanent". Table 1 gives a summary on the different forms of AF. (2, 7)

Form of AF	Definition
Initial event	First documented episode of AF
Paroxysmal (PAF)	Spontaneous termination <7 days, cardioversion of an episode lasting less than 7 days
Persistent (PSAF)	Duration >7 days, cardioversion of at least 1 episode lasting more than 7 days
Long-standing Persistent (LSPAF)	Duration >1 year
Permanent	AF is accepted by patient and physician; no further rhythm control therapy is undertaken

Table 1: Clinical classification of AF. (2, 7)

There are several diseases leading to AF with most cases attributed to cardiovascular causes. In about a third of patients there is no heart disease present or any disease at all. (8) These forms of AF have been historically described as “lone AF” and “idiopathic AF” respectively and have commonly been used as synonyms. As the definition of these terms is inconsistent and no clear guidelines regarding management of these patients are given, it is recommended to avoid these terms altogether. (2, 9) Section 1.1.3 Pathophysiology provides more information on other causes and the etiology of AF.

Arrhythmias associated with AF

Atrial flutter (AFL) is a form of supraventricular tachycardia, which is regular in nature. Atrial frequencies are about half of the ones with atrial fibrillation, usually varying between 250 and 350 bpm. Characteristic ‘flutter waves’ and a ‘saw tooth’ pattern, that can be seen in ECG leads II, III and aVF, are diagnostic. In most cases ventricular frequencies are much lower due to an accompanying 2:1 AV block, typically under 150 bpm. AFL often occurs in mixed forms with AF and can further along also deteriorate into AF. (7)

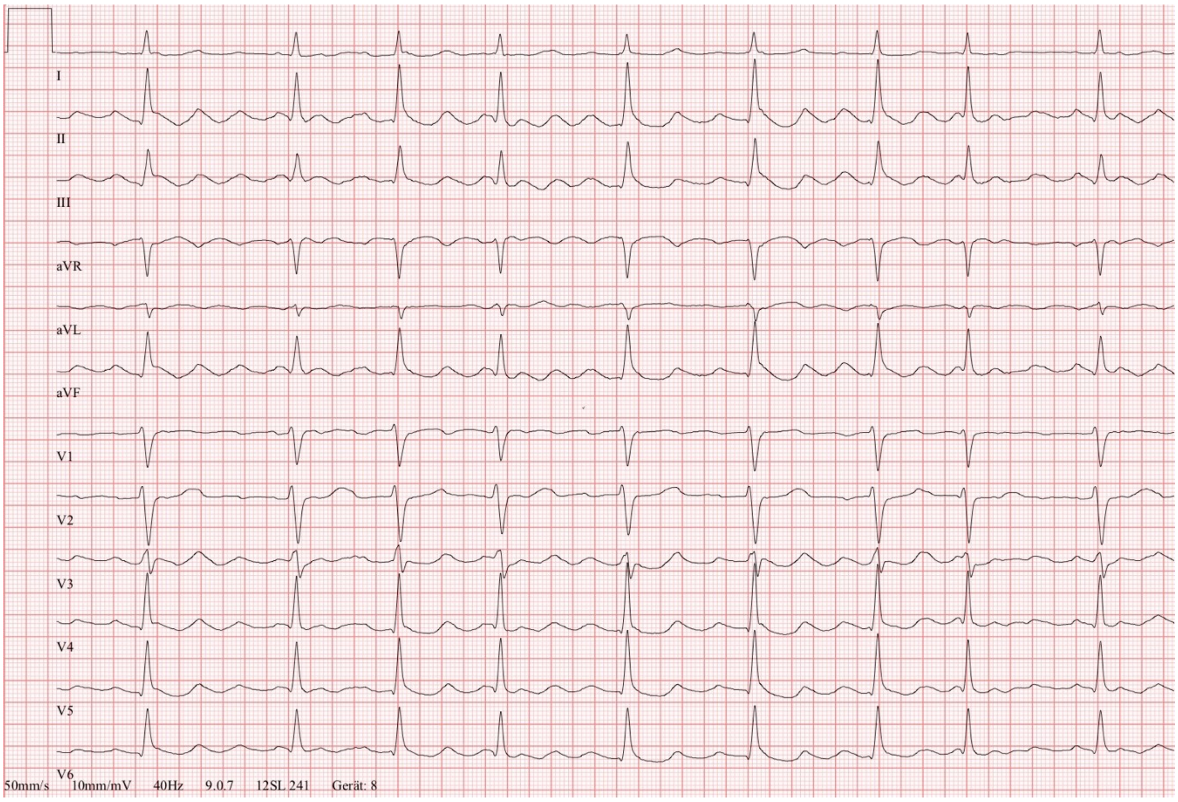

Figure 2: ECG showing atrial flutter (AFL). By courtesy of Dr. med. univ. Martin Manninger-Wünscher.

Atrial tachycardia (AT) has distinct P waves that are separated by an isoelectric baseline in all ECG leads. Electric signals from the atrium are transmitted 1:1 to the ventricle, therefore frequencies range from 100 to >300 bpm. (7)

1.1.2 Epidemiology

Prevalence and Incidence

Atrial fibrillation is the most common sustained arrhythmia in adults. (1) This arrhythmia is prevalent in approximately 3% of adults aged 20 and older, (10) every 4^{th} person will develop atrial fibrillation in their life. (2, 11, 12)

In 2010, estimates suggested a prevalence of 387,7 in women and 660,9 in men per 100.000 population of all ages in developed countries, therefore making AF more frequent in men than women. The same is true for the incidence rate, which was projected at 90.4 in women and 123.4 in men per 100.000 person years of all ages in developed countries. AF prevalence as well as the incidence rates have increased globally and even more so in developed countries in the period of 1990 until 2010. (13)

AF is more present in older people. (12-14) The prevalence rate increased from 0,9% in persons <55 years to 9,0% in persons >80 years. It is estimated that by the year 2050, there will be a more than two-fold increase in the prevalence of AF. (12, 14) This increase is led back to an improvement of AF screening methods (15) as well as the ageing of population and factors predisposing atrial fibrillation. (16)

Risk Factors

Major Factors predisposing an increased risk of AF include male gender, increasing age, arterial hypertension, obesity, type 2 diabetes, hyperthyroidism, smoking, valvular heart disease, acute coronary syndrome and chronic heart failure. (11, 17-19) Table 2 shows the corresponding Odds Ratios and Hazard Ratios for a few of these factors. While ACS, hypertension and male gender had the greatest impact on the development of AF, obesity seems to have the lowest. (11)

Several other factors including use of alcohol and increased biomarkers such as CRP and BNP have also been suggested. (17)

Some studies also reported an elevated risk of AF following exercise on a regular basis for several years. The effect was observed primarily in male joggers under 50 years with no detectable difference in risk of AF to general population above that age. (20, 21)

Risk factor	Odds Ratio [95% CI]
Arterial hypertension	1.73 [1.31, 2.28]
Male gender	1.64 [1.45, 1.86]
Smoking	1.47 [1.22, 1.78]
Diabetes type 2	1.44 [1.07, 1.94]
	Hazard Ratio [95% CI]
ACS	1.77 [1.44, 2.19]
Hyperthyroidism	1.68 [1.29, 2.18]
Obesity	1.22 [1.14, 1.30]

Table 2: Odds Ratios and Hazard Ratios for risk factors predisposing AF. (11)

Morbidity and mortality

Hospitalization is common in patients with atrial fibrillation. Approximately 31% had at least 1 hospitalization per year while 10% had 2 or more. Cardiovascular causes account for around half of the admissions. The most important complications of AF are stroke and heart failure. (22)

There is a five-fold increase in risk of stroke among patients with independent AF, while the simultaneous occurrence of AF in heart failure or CAD doubled the risk of stroke in men and trebled the risk in women respectively. (23) A third of the patients, who suffered a stroke, already have or are newly diagnosed with AF. (2) Furthermore, AF is also often the cause of cryptogenic stroke. (23)

Even without the presence of stroke AF has a negative effect on cognitive function. (24) The underlying cause seems to be microthrombotic events, which occur due to AF patients' hypercoagulability. (24, 25)

The simultaneous occurrence of AF and heart failure is a complicated matter, since both disorders aggravate each other. There is an association between the severity of heart failure and the occurrence of AF. (26) This topic is discussed further in section 1.3 Atrial fibrillation and Heart Failure.

Risk of death for patients with isolated AF is doubled among women and there is a 1.5-fold increase among men, although concomitant diseases often result to a much higher mortality. (27)

1.1.3 Pathophysiology

When discussing the pathophysiological mechanisms associated with AF, three values in the development of action potentials (AP) are of interest:

1. The stability and value of the resting potential, which is maintained by Ca^{2+}- and K^{+}-ion-channels
2. The length of the action potential and refractory period
3. The conduction velocity

Changes in these values lead to *focal ectopic activity* and *reentry* phenomena in the atrium, which are known as *triggers* initiating AF. Fixed changes in the structure of the atrium (*atrial remodeling)*, acute ischemia and scar tissue are *substrates* for triggers, thus causing AF progression and more persistent forms. (28)

Focal ectopic activity

This type of irregular activity describes sudden and irregular AP emerging from outside the sinus node, typically a single location in the left atrium. They are the products of "delayed afterdepolarizations (DAD)" and "early afterdepolarizations (EAD)". DAD occur as a result of pathological diastolic Ca^{2+} release of the sarcoplasmic reticulum in atrial myocytes. The mechanism is highly complex in its molecular pathway, though basically, through this process an inward current (which normally occurs during initial depolarization) is created in the refractory phase of the AP, therefore causing an additional depolarization before the next regular AP occurs. If the DAD is high enough, an ectopic beat is triggered. EAD on the other hand, stem from pathologically prolonged AP duration (and therefore longer refractory period). The longer duration leads to inward Ca^{2+} currents and an additional depolarization in the refractory period. (28)

Ectopic activity typically emerges from around the four pulmonary veins and represents the cause of PAF in 94% of cases. Consequently, the pulmonary veins are the most common target of catheter ablation. (29, 30)

Reentry

Reentry occurs when atrial myocytes are excited in a reversed manner through regular or ectopic beats for a second time after initial depolarization. Contrary to EAD, the underlying cause lies in a shortened AP duration or lower conduction velocity through anatomical changes in the myocardium. In normal atrial tissue AP duration and conduction velocity are balanced in a way, that allows the potential to travel through the atria and reach each myocyte, while not depolarizing them for a second time in the same beat. When AP duration and therefore also the refractory period are reduced severely, the myocyte becomes excitable before the potential has passed on to cells not in the immediate vicinity, thus allowing it to be depolarized for a second time in the same regular beat. The same effect applies when AP conduction is slowed. Both lead to circling electrical activity, the initial AP "reenters" in atrial tissue with the mentioned pathological conduction characteristics and causes additional beats. Reentry associated with AF can take place from one single source (*single-circuit*) or multiple (*multiple-circuit*). (28)

The *leading circle concept* (31) and the *rotor* (or *spiral wave reentry*) *concept* (32) are theories describing functional reentry, meaning the absence of anatomical changes to the myocytes. The *multiple wavelet hypothesis* (33) proposed by Moe et al. in 1964 is a widely accepted theory and currently subject to debate. (34) Reentry in general is recognized as a factor for sustaining AF and therefore often found in more severe forms of AF. (30)

Genetic predisposition

Inheritable factors seem to have a substantial influence on the occurrence of AF. One study found that persons had a significantly higher risk of AF, when a first- or second-degree relative themselves were diagnosed with that tachycardia. This risk increased even further when there were two affected relatives. (35) Certain genetic variants of the Pitx2 (paired-like homeodomain transcription factor 2) gene located on chromosome 4q25 have been associated with an estimated 5-fold risk increase for developing AF. (36) This gene is vital in cardiac development, specifically also in the development of the pulmonary veins, which are a common source of ectopic activity. Other gene variants lead to altered activity in Ca^{2+}- and K^{+}- channels and therefore causing delayed afterdepolarizations. (28)

Atrial remodeling (ATR)

ATR describes structural transformations and alterations in electrical properties of the atrium. It is induced by rapid tachyarrhythmia over a period of several years, while all the changes promote mechanisms causing AF in the process and therefore create a vicious circle, which leads to more severe forms of AF. Since similar types of ATR are also found in other cardiovascular diseases such as hypertension and CHF, the process is accelerated even further, when one or more of these conditions is present alongside AF. (30)
The electrical features of myocytes are altered by AF in a way that shortens the duration of AP, thus increasing the likelihood of reentry phenomena. This is the result of a downregulation of inward Ca^{2+}- channels and increased activity of inward K^{+}- channels. Pathological Ca^{2+} handling entails a reduction in atrial contractility, which leads to atrial

dilation. Atrial dimensions have been found to be a good prognostic factor on the severity of AF, as the larger size favors the occurrence of multiple-circuit reentry.
Structural transformations in the atrium include proliferation of fibroblasts and increase in extra-cellular matrix (*fibrosis*), fatty infiltration and inflammatory reaction, which in AF occur reactively through increased wear on the atrium or reparative as a result of replacing patches of necrotic tissue. Consequently, the myocytes are separated from each other, thus leading to more loose electrical connections. Transformed tissue exhibits longer conduction path lengths and slowed conduction time, all of which act as a substrate for reentry mechanisms.
Studies have found Angiotensin II to promote atrial fibrosis in many cardiovascular diseases. With this mechanism in mind, it becomes clear why ACE-inhibitors lead to a general reduction in atrial remodeling and a better prognosis in AF-patients. (30, 37)

Thrombogenesis

AF predisposes through various mechanisms the formation of thrombi in the atria, hence increasing the risk of the stroke. While more persistent forms of AF present a greater risk, even short and rare episodes of paroxysmal AF seem to activate the mechanisms leading to blood clots. The occurrence of stroke is responsible for a great fraction of the mortality among AF patients. (27)

It is commonly understood that Virchow's triad is a plausible theory on thrombogenesis and also valid in AF. According to the theory, three factors attribute to a prothrombotic milieu: changes in hemodynamics, endothelial dysfunction or damage, and hypercoagulability.
The left atrial appendage (LAA) is a pouch with a narrow opening in the wall of the left atrium, which predisposes the formation of clots through greatly reduced blood flow into this region, with the blood sometimes even coming to a complete stop. Consequently, it is by far the most common source of atrial thrombi. This alteration of hemodynamics takes place in the other parts of the atria as well, since general contractile dysfunction as a result of AF causes turbulence in blood flow and in some parts even stasis, as is evident in the LAA.
Atrial remodeling contributes to endothelial defects and therefore further elevates prothrombotic milieu. The underlying mechanism seems to be a "roughing process" of the endocardium and changes in the extracellular matrix of atrial tissue, which presents the base for the formation of blood clots. Von-Willebrand factor, which acts as surrogate for

endothelial damage, has been found to be elevated in patients with AF and therefore supporting this theory.
Studies have found that AF also leads to inflammation with increased levels of interleukin 6 (IL-6) and high-sensitive C-reactive protein (hs-CRP), which in turn furthers platelet activation and atrial remodeling. It is well described that AF itself also activates various proteins in the coagulation cascade.
Lastly, other diseases often associated with AF (eg. congestive heart failure or valvular disease) also promote the above given prothrombotic mechanisms and hence increase the risk of stroke even further. (38, 39)

1.1.4 Management and therapy

1.1.4.1 Recommendations according to Evidence Based Medicine

In order to make recommendations on diagnostic and therapy decisions more traceable, expert societies have used the "level of evidence" and "class of recommendation", They are the cornerstones of Evidence Based Medicine (EBM) as they describe the source of the information, which is used for the guidelines, and the strength of the recommendation. (40)
Table 3 and Table 4 show common systems, which are also used by the European Society of Cardiology (ESC) and the Northern American expert societies (American Heart Association - AHA, American College of Cardiology ACC, Heart Rhythm Society – HRS). The recommendations on the management of AF are composed by these societies and updated according to the findings in recent research. An outline will be given in the following chapter. (2, 17)

Level of evidence	Definition
Level A	Data is derived from several randomized clinical trials or meta-analyses
Level B	Data is derived from a single randomized clinical trial or large non-randomized trial
Level C	Expert consensus or data derived from registries or retrospective studies

Table 3: Levels of evidence. (2, 17)

Class of recommendation	Definition “used wording”
Class I	Clear evidence that a form of treatment is beneficial. Benefit outweighs risk by far. **“is recommended”**
Class IIa	Evidence suggests a form of treatment is beneficial, though there is conflicting data. Benefit outweighs risk. **“should be considered”**
Class IIb	Evidence slightly in favor of a treatment’s usefulness, there is even more conflicting data. Benefit outweighs risk by a margin or is equal. **“may be considered”**
Class III	Evidence that a form of treatment is not useful/ineffective or even causes harm. **“is not recommended”**

Table 4: Classes of recommendation. (2, 17)

1.1.4.2 Prevention

Risk factor management

There are several cardiovascular diseases and associated conditions, which have been identified to predispose the development of AF (see also 1.1.2 Epidemiology). Among these are also classic risk factors precipitating or worsening many cardiovascular conditions in return. For this reason, risk factor management not only lowers the risk of AF but is beneficial for the overall health of patients as well. (2) In the following, an overview of the most influential risk factors is given. Heart Failure is described in section 1.2 and its correspondence with AF in section 1.3.

Arterial Hypertension has been found to further increase the risk of stroke and lead to higher AF recurrence. ACE inhibitors or ARBs are an established first-line therapy in the treatment of hypertension and effectively reduce structural remodeling and the number of episodes in patients with AF. (41)

Valvular heart disease often entails AF. About one third of AF patients are diagnosed with some form of this disease. (42) Through complementing pathophysiological mechanisms such as volume and pressure overload, valvular heart disease causes AF progression and vice versa. For this reason, valve replacement or repair is to be considered even more in severe forms when AF is present as well, even though the patient might be oligosymptomatic. (43)

Diabetes mellitus mainly conveys an increased stroke risk in AF patients. The risk increases with the longevity of diabetes onset. However, intensive blood sugar control does not seem to have a direct effect on AF progression, but may still be influenced indirectly through risk reduction of concomitant cardiovascular diseases. (44)

Obesity has been identified to increase the incidence of AF, with the body mass index (BMI) being directly proportionate to the risk of AF. A weight reduction of 10 to 15 kg leads not only to reduced AF occurrence, but also to less (severe) symptoms associated with AF. It is also important to note that obesity is linked to a higher complication rate during and a higher relapse rate after AF ablation procedures (see section 1.1.5 Catheter ablation). (45, 46)

Obstructive sleep apnoea causes fluctuations in intrathoracic pressure and vagal stimulation, thus shortening action potentials in the atrium and predisposing the occurrence of AF. In such patients, continuous positive airway pressure (CPAP) ventilation can reduce the severity of the apnoea and consequently also the number of AF episodes. Therefore, actively searching for obstructive sleep apnoea has been deemed reasonable and should be considered in AF patients. (47)

Chronic kidney disease (CKD) is relevant to the outcome of AF patients, as it defines the dosage of oral anticoagulation and some antiarrhythmics. In many trials on this matter, a cutoff value of <50 mL/min creatinine clearance (as a surrogate for CKD) has been chosen in order to adapt dosage of novel oral anticoagulants (NOAC). For this reason, the ESC stated the following:

"*The assessment of kidney function by serum creatinine or creatinine clearance is recommended in all AF patients to detect kidney disease and to support correct dosing of AF therapy. I A recommendation*" (2)

Stroke risk stratification - the CHA_2DS_2-VASc score

The risk of stroke is increased 5-fold with AF on its own, which also conveys a higher mortality in such patients (see chapter 1.1.2 Epidemiology). *Oral anticoagulants (OAC)* are an effective treatment for the prevention of stroke events in patients with AF, but also predispose a higher chance of bleeding. (2, 48, 49) When treating patients with OAC, stroke prevention must be weighed against the risk of bleeding. In this case, the benefits of anticoagulation in stroke prevention against the relatively low risk of bleeding almost always tip the balance in favor of OAC though. (2, 17)

In recent years the *CHA_2DS_2-VASc score* has been a widely used tool for measuring the risk of stroke in AF patients, as it has proven itself in randomized clinical trials and found its way into cardiology guidelines. (50, 51) Based on data from epidemiological studies, the score uses several known risk factors for embolic events (Table 5) in order to give a percentage on the annual likelihood of a stroke occurring (Table 6). A total of 9 points can be achieved, since the age-factors are mutually exclusive.

"The CHA_2DS_2-VASc score is recommended for stroke risk prediction in patients with AF. I A recommendation" (2)

	Risk factor	Points
C	**C**ongestive heart failure (Overall reduced ejection fraction (≤40 %) or signs of heart failure)	1
H	**H**ypertension (Blood pressure over 140/90 mmHg in 2 separate measurements or treated hypertension)	1
A_2	**A**ge ≥75 years	**2**
D	**D**iabetes Mellitus	1
S_2	**S**troke, transient ischemic attack or thromboembolism in past medical history	**2**
V	**V**ascular disease (myocardial infarction, peripheral artery disease or aortic plaque in past medical history)	1
A	**A**ge 65-74 years	1
Sc	**S**ex **c**ategory (female)	1

Table 5: Definition of the CHA_2DS_2-VASc score. (50)

CHA_2DS_2-VASc	Annual stroke risk in %
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

Table 6: Annual stroke risk according to CHA_2DS_2-VASc score. (52)

Furthermore, the ESC recommends initiating OAC-therapy at a CHA_2DS_2-VASc score of 1 and more in men and 2 or more in women. Following this scheme, every AF patient being 75 years old or older should receive anticoagulation therapy, even when there are no other risk factors present. In patients having only one risk factor (meaning a score of 1 in men and 2 in women) there is controversial data about the effectiveness of anticoagulation. Although some evidence suggests that it can be beneficial, refraining from OAC in agreement with the patient is also a valid option. Low risk patients (0 points in men and 1 point in women) should not be receiving anticoagulation therapy. It is noteworthy to mention that only patients <65 years old with lone AF qualify for this last category. (2)

Bleeding risk stratification - the HAS-BLED score

Similar to the CHA_2DS_2-VASc score with stroke risk, the *HAS-BLED score* was developed to assess the yearly risk of major bleeding in AF patients treated with anticoagulants. Major bleeding was defined as intracranial bleeding, hospitalization due to bleeding, hemoglobin decrease >2 g/dL or need for transfusion. Since risk factors for stroke and bleeding overlap, the HAS-BLED score is built up of similar components as the CHA2DS2-VASc score. Nevertheless, the goal of the HAS-BLED score is not to provide a tool for comparison against stroke risk in patients receiving OAC, but rather allowing an estimate of bleeding risk and encouraging to modify predisposing risk factors. Patients with a score of ≥3 are classified as "high risk" and should be monitored more closely (eg. frequent review of anticoagulation therapy). (53)

"Bleeding risk scores should be considered in AF patients on oral anticoagulation to identify modifiable risk factors for major bleeding. IIa B recommendation" (2)

	Risk factor	Points
H	**H**ypertension (uncontrolled, >160 mmHg systolic)	1
A	**A**bnormal renal function (need for dialysis, post-transplant or Creatinine >200 µmol/L)	1
	Abnormal liver function (present cirrhosis or bilirubin >2x normal and AST, ALT, AP >3x normal	1
S	**S**troke in past medical history	1
B	**B**leeding (major bleeding in past medical history or predisposition to bleeding)	1
L	**L**abile INR (unstable, elevated; <60% time inside therapeutic range)	1
E	**E**lderly (> 65 years old)	1
D	**D**rugs (use of medication predisposing to bleeding, eg. antiplatelet agents, nonsteroidal anti-inflammatory drugs)	1
	Alcohol (Alcohol or drug usage in past medical history, ≥ 8 drinks per week)	1

Table 7: Definition of the HAS-BLED score; AST = Aspartate transaminase, ALT = Alanine aminotransferase, AP = Alkaline phosphatase. (53)

1.1.4.3 Stroke prevention

Vitamin K antagonists (VKAs)

These anticoagulants have been used in the prevention of stroke in AF patients for many years, with a good amount of data already collected on their efficacy. In most conducted studies the VKA Warfarin was used with the observed effect amounting to a two-thirds decrease of stroke risk and one-third mortality reduction when compared to Aspirin or no prevention at all. (54) Since Warfarin was not legally approved in Austria, Acenocoumarol or Phenprocoumon are used alternatively. (55)

VKAs require close monitoring and dose adaptation according to the most recent value of the international normalized ratio (INR) in order to provide the best outcome. A low INR means inadequate anticoagulation, while an elevated one leads to greater risk of bleeding. This sometimes proves quite difficult, as comorbidities, genetic variants, diet, other medication and lack of patient compliance all have an influence on the cumulative dose and the metabolism of the VKA. The efficacy of the therapy is dictated by the time spent in the optimal INR interval. Following their mechanism of action, all VKAs can be antagonized by a dose of vitamin K. (52) It is recommended to utilize VKAs as a means of anticoagulation in patients with valvular AF (atrial fibrillation with concomitant rheumatic valvular disease or mechanical heart valves). (2)

"Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves. I B recommendation" (2)

Novel oral anticoagulants (NOAC)

As the name suggests, NOAC have been introduced only recently in the treatment of AF patients with risk of stroke. Namely Apixaban, Rivaroxaban, Edoxaban and Dabigatran, these substances have a slightly different mode of action than VKAs, hence certain benefits arise from the use of these anticoagulants: First and foremost, there is no need for frequent monitoring, the appropriate dosages have been carefully selected in large randomized trials for each active agent. Secondly, there has also been reported a statistically significant difference in favor of NOAC in the effect on stroke prevention, fewer incidents of major bleeding and mortality reduction when compared to Warfarin. (56-59) One meta-analysis on the subject showed an overall 19% decrease in the occurrence of stroke (RR 0.81; 95% CI 0.73-0.91; $P < 0.0001$) and a 10% lower mortality rate (RR 0.90; 95% CI 0.85-0.95; $P=0.0003$) in patients receiving NOAC. (60)
Apart from Dabigatran, NOAC are not antagonizable, which is also a big drawback in comparison with VKAs. Because of their superiority in terms of effectiveness and lower risk of bleeding the ESC recommends favoring NOAC over VKAs regardless. (2)

"When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist. I A recommendation" (2)

Left atrial appendage occlusion

This procedure can be performed in two ways: an umbrella-like device is implanted in the left atrium by an interventional cardiologist or the left atrial appendage (LAA) is closed off through ligation in open surgery. The goal is to exclude the LAA from the cardiovascular system and therefore remove the primary source of intracardial thrombi.
There is limited evidence suggesting the interventional occlusion device is non-inferior in stroke prevention when compared to Warfarin, but possibly also with fewer major bleeding. Though initial results seem promising, further investigation is needed on implantation success rates and complication rate. Therefore, the left atrial appendage procedure remains a reserve option for AF patients with contraindications to oral anticoagulation. (2, 61, 62)

"LAA occlusion may be considered for stroke prevention in patients with AF and contra-indications for long-term anticoagulant treatment (e.g. those with a previous life-threatening bleed without a reversible cause). IIb B recommendation" (2)

1.1.4.4 AF-specific therapy

Symptom burden – EHRA symptom scale

The experienced symptoms with AF range from mostly asymptomatic to severe limitations in the daily routine and are associated with a lower quality of life. Individual symptoms such as palpitations, syncope, dyspnea (on exertion) and chest tightness have been reported. In order to objectify these in AF patients the European Heart Rhythm Association has developed a symptom scale (see Table 8). While there were initially only four, classes 2a ("no influence on daily activity") and 2b ("patient troubled by symptoms") have been added in a follow-up study, as these might represent an important threshold for decisions regarding rate or rhythm control therapy. (63) Furthermore, a retrospective analysis found out 61.8% of AF patients were symptomatic (meaning EHRA ≥2) and 16.5% had severe symptoms or even a discontinued daily routine (EHRA 3 or 4). (2, 64)

EHRA score	Symptoms	Definition
1	None	Asymptomatic AF
2a	Mild	Daily routine not affected by AF symptoms
2b	Moderate	Daily routine not affected; AF symptoms perceived as troubling by the patient
3	Severe	Normal daily routine affected by AF symptoms
4	Disabling	Normal daily routine discontinued

Table 8: modified EHRA symptom scale. (2, 63, 64)

Acute therapy

Sudden onset of AF or an episode of preexisting PAF may require therapeutic intervention, especially when symptomatic. There are several validated treatment options, which can be divided into two basic forms: Rate control, which translates to lowering the heart rate to an acceptable level, and rhythm control, meaning the conversion to sinus rhythm.

Acute rate control. As symptoms might be caused by an elevated heart rate in itself, this course of action provides adequate relief for mildly symptomatic and hemodynamically stable patients. Beta-blockers and the calcium-antagonists diltiazem and verapamil are the overall most effective options, (65, 66) concomitant conditions might require a different approach though: In patients with heart failure and reduced ejection fraction (HFrEF), cardiac glycosides (available as digoxin or digitoxin) should be preferred over calcium-antagonists, as these exhibit a negative inotropic effect. (67)

Pharmacological cardioversion. Cardioversion becomes necessary in patients with adequate rate control and the persistence of severe symptoms. Restoration of sinus rhythm through antiarrhythmics is effective in about half of patients with acute AF. Unlike electrical cardioversion, it does not require neither sedation nor fasting. (68) Studies have proven propafenone and flecainide effective at pharmacological cardioversion, but they are limited to patients without structural heart disease. Amiodarone can be used as an alternative in patients with heart failure and ischemic heart disease. (69, 70)

"Pill in the pocket" concept. With this approach, patients can self-administer a single dose of oral propafenone or flecainide. It is only slightly less effective than cardioversion in a hospital, but in turn practical and reassuring to patients. (2)

Electrical cardioversion is quicker and more efficient in restoring sinus rhythm compared to pharmacological but requires appropriate sedation with close monitoring in order to be performed safely, hence it is the preferred choice of action for hemodynamically unstable AF patients. Biphasic defibrillators are superior to monophasic in comparison and electrodes should be placed anterior-posterior. (71) It is necessary to begin anticoagulation before electrical cardioversion in patients with an AF episode lasting longer than 48h, as the cardioversion poses a great risk for thromboembolic events. The ESC recommends starting at least 3 weeks before the planned procedure and continuing until 4 weeks after. Should electrical cardioversion be needed sooner, transesophageal echocardiography (TOE) can be performed in order to rule out thrombi in the left atrium. (2)

Long-term therapy

Rate and rhythm control are both valid treatment options in the long-term therapy of AF. All studies so far have found no statistically significant evidence favoring a combination of rhythm and rate control over rate control by itself. (72) The development of modern rhythm control strategies might have tipped the balance, although more trials are needed in the future to confirm this difference. (2)

Long-term rate control. It is recommended to take a lenient approach on rate control with a heart rate of <110 bpm, since studies could not show a significant benefit with stricter and lower rate control schemes. Beta-blockers should be used primarily for their overall good tolerability, while verapamil and diltiazem might be a better choice for physically active and athletic patients, as, unlike beta-blockers, calcium antagonists improve the capacity for exercise. (73) Unfortunately, beta-blockers seem to lose the mortality benefit in patients with heart failure and simultaneous AF. (74) As stated before, calcium antagonists are contraindicated in patients with HFrEF. Digitalis is a reasonable alternative to beta-blockers, but is generally prescribed to sicker patients, as one observational review showed. (75) Often a combination therapy is required to reach heart rate targets. (2)

Atrioventricular node ablation and pacing describes catheter ablation of the AV node (meaning the atria are electrically cut off from the ventricles) and the consequent implantation of a VVI-pacemaker. It is an established rate-control procedure with a low complication rate but should only be performed as a measure of last resort if no adequate rate control can be achieved with drugs and rhythm control is not feasible, since it renders the patient permanently dependent of a pacemaker. (2)

"Beta-blockers, digoxin, diltiazem, or verapamil are recommended to control heart rate in AF patients with LVEF ≥40%. Beta-blockers and/or digoxin are recommended (...) with LVEF <40%. I B recommendations" (2)

Long-term rhythm control. If patients remain symptomatic despite optimal rate control, a treatment involving rhythm control should be introduced. Sinus rhythm is maintained longer with antiarrhythmics compared to placebo, though with moderate effect. It is important to note that antiarrhythmic drug therapy offers no statistically significant reduction in mortality or cardiovascular events, but on the contrary slightly increases hospitalization rate in AF patients. (72, 73) Therefore, the intake duration of antiarrhythmics should be kept to the necessary minimum required for an improvement in AF-related symptoms.

First-line antiarrhythmics include propafenone, flecainide, dronedarone and sotalol. In patients with heart failure or other contraindications for these drugs, amiodarone can be used as an alternative, but should remain a secondary option in healthy patients because of its extracardiac side-effects. All mentioned antiarrhythmics may cause life-threatening arrhythmia, for this reason it is recommended to perform ECG-monitoring upon initiation. Catheter ablation presents an alternative to antiarrhythmic drug treatment and will be discussed further in the following chapter. (2)

"The choice of AAD needs to be carefully evaluated, taking into account the presence of comorbidities, cardiovascular risk and potential for serious proarrhythmia, extracardiac toxic effects, patient preferences, and symptom burden. I A recommendation" (2)

Surgical Ablation. Rhythm control can be achieved surgically through the Cox-Maze-procedure. In this procedure, a series of ablation lines is created using bipolar radiofrequency or cryothermy similarly to catheter ablation, which aim to isolate ectopic triggers and prevent reentry mechanisms in the left and right atrium. The LAA is occluded as well to mitigate the risk for thromboembolic events. The corresponding regions are accessed through open-heart-surgery when combined with other procedures such as valve replacement or coronary artery bypass graft (CABG) surgery, or mini-thoracotomy as a thoracoscopic stand-alone procedure. (2, 76) Patients who underwent the first showed fewer AF occurrences compared to no AF surgery, but were more likely to require pacemaker implantation. (77) Stand-alone thoracoscopic AF ablation could be promising in patients with relapse after initial catheter ablation, as comparative studies suggested it being more effective in such patients. (78, 79) Currently the expert consensus on surgical and catheter ablation recommends performing concomitant AF surgery as first or second-line treatment in AF patients undergoing mitral valve surgery (I B recommendation) and only as second-line with CABG surgery (I B). A stand-alone thoracoscopic procedure may be considered after insufficient rhythm control with AAD (IIb B in PAF, IIa B in persistent and long-standing persistent AF). (76)

1.1.5 Catheter ablation

Catheter ablation is an interventional procedure with the goal of long-term AF rhythm control. It has gained increased recognition in recent years and presents the primary alternative to AAD treatment. This fairly complicated procedure should be performed in specialized centers by an experienced electrophysiologist in order to achieve comparable results to the ones in randomized trials as well as a low rate of complications. (76)

Indications

The main benefit of catheter ablation is to reduce symptoms such as fatigue, palpitations and exercise intolerance and increase quality of life in AF patients. Thus, symptomatic AF is the primary requirement for the procedure. It is better suited for patients with PAF, with an increasing recurrence rate in more persistent forms. Several other factors such as patient age, obesity or heart disease have been associated with a lower chance of success and higher probability for the occurrence of complications, therefore limiting the use of the procedure in such patients (further information on the outcome of catheter ablation is provided in chapter 3.3). (76)

Patients with Tachy-Brady-Syndrome, a special form of arrythmia associated with AF, show alternating heart frequencies, which limit the use of AAD due to bradycardia. Similarly, AAD are often to be avoided in athletic AF patients. Therefore, catheter ablation should be considered as the initial choice of action in such patients. (76)

Catheter ablation was initially recommended after AAD treatment failure, but since recent data has shown promising results, it might also be considered as the overall first-line treatment in AF patients. (80, 81) One meta-analysis analyzed the success rate compared to AAD and showed significantly fewer AF recurrence with catheter ablation. (82) More data is needed though to affirm these observations. Lastly, the patient preference should also be taken into account when deciding for the best course of action, as some might prefer a conservative AAD treatment over an interventional procedure and vice versa. (76)

To summarize, the following recommendations are stated in the 2017 expert consensus statement for the use of catheter ablation, which are largely in accord with the 2016 ESC guidelines:

"Symptomatic AF refractory or intolerant to at least one Class I or III antiarrhythmic medication:

Paroxysmal: Catheter ablation is recommended. I A
Persistent: Catheter ablation is reasonable. IIa B
Long-standing persistent: Catheter ablation may be considered. IIb C

Symptomatic AF prior to initiation of antiarrhythmic therapy with a Class I or III antiarrhythmic medication:

Paroxysmal: Catheter ablation is reasonable. IIa B
Persistent: Catheter ablation is reasonable. IIa C
Long-standing persistent: Catheter ablation may be considered. IIb C" (76)

Technique

The goal of catheter ablation is either to electrically isolate or modify certain regions in the atria acting as triggers or substrates for reentry and thus stop conduction of irregular and tachycardic rhythm. Traditionally, this is achieved by inserting a transvenous catheter into the femoral vein, applying radiofrequency energy (RF) and the consequent resistive heating of atrial tissue. The resulting lesions need to reach deep into the myocardium for a long-term electrical isolation. Those lesions can be adapted in size and depth through the regulation of contact force, power, impedance, temperature and duration: High energy and good contact between catheter and endocardium leads to better procedure efficiency, but tissue temperature needs to be monitored closely. If temperatures exceed 100°C uncontrolled myocardial damage and even perforation through sudden release of steam ("steam pop") can occur. Impedance must be kept low in order to ensure adequate power delivery and contact force; it might increase as debris builds up with high heat at the catheter tip after some time of use. This can be minimized through the utilization of special catheter coatings with passive cooling properties. (83)

A longer duration of energy application results in better penetration of deeper myocardial layers, but also bears the risk of affecting non atrial tissue (eg. esophagus or phrenic nerve). Therefore, RF energy is applied for a shorter period in thinner regions of the atrium. (76, 84)

AF is most commonly caused by ectopic activity located at the insertion points of the pulmonary veins (PV) into the left atrium, hence *pulmonary vein isolation (PVI)* forms the cornerstone of catheter ablation. This can be achieved through the placement of circular lesions around the left and right PV pair using RF ablation. It is essential to obtain complete electric isolation, as any gap in the lesions can cause reconnection of the PVs and AF recurrence as a result. (I A recommendation). (76, 85-87)

Once PVI is completed, it is recommended to monitor electrical activity in the PV antrum using a special mapping catheter. The absence of action potentials stemming from the PV marks the endpoint of the ablation procedure and the lesion set is regarded complete (*entrance conduction block*). (I B recommendation). (76)

Alternatively, ectopic activity or arrhythmia can be documented within the isolated PV during continuous sinus rhythm (*exit conduction block*) or pacing along the circular lesions to reveal remaining gaps (*loss of pace capture*) be performed. (88) Another method to demonstrate permanent PVI is to administer adenosine, which can unmask dormant PV reconnection. (IIb B recommendations for exit conduction block, loss of pace capture and utilization of adenosine). (76, 89)

Nevertheless, in order to ensure successful PVI a waiting time of 20-30 minutes should be considered before concluding the procedure, as possible reconnections mostly occur 30 minutes after completion of the lesion set. (IIb B recommendation). (76, 90)

PVI can also be attained with cryoballoon (CB) catheters, which use liquid N_2O to freeze atrial tissue and cause transmural lesions. Studies have shown comparable success rates to RF ablation, making CB ablation a viable alternative. (91)

The cavotricuspid isthmus is a frequent source of atrial flutter (AFL). If there is documented AFL present in AF patients undergoing catheter ablation and the AFL can be connected to the cavotricuspid isthmus, it is recommended to induce a linear lesion in this very region. *Cavotricuspid isthmus ablation* is the second most performed technique and often used in combination with PVI. (I B recommendation). (76, 92)

Other regions have been identified as sources of arrhythmia and are used as lesion sites. These involve a roof line (cranial connection between PV lesions) and mitral isthmus line (connection of left PV lesion and mitral valve) as linear lesions and one lesion encircling the superior vena cava, to give a few. Currently, there is insufficient evidence on the effectiveness of these and other not mentioned ablation targets. (76)

Outcome

The main goal of ablation is to permanently stop AF occurrence, significantly reduce symptom burden and therefore improve quality of life for AF patients altogether. Catheter ablation is preferably performed in patients with PAF with most comparative studies to AAD being also conducted in such patients, as a longer duration of continuous AF is associated with a lower procedure success rate and shorter AF free intervals after ablation. Thus, further investigation is needed in patients with more persistent forms of AF. (93)

As stated before, catheter ablation is primarily indicated in AF patients as second-line rhythm-control after AAD therapy failure. Multiple clinical studies compared the outcome of ablation with mainly PVI (additional lines were allowed in these trials though) to continuous AAD therapy, showing significantly higher AF freedom rates of 59-89% after 12 months with catheter ablation as opposed to 5-23% in patients who received AAD. Hence these results lead to catheter ablation being commonly recognized as superior to AAD and a well-established and safe second-line option for rhythm control. However, a great deal of these studies was done on young patients with few comorbidities, which might be a limiting factor when considering ablation therapy in elder patients. (94)

In recent years, several trials have also investigated catheter ablation as first-line rhythm control therapy. In the MANTRA-PAF trial, recurrence rates in patients with PAF over a period of 2 years assessed with the result of significantly lower AF recurrence of 15% with catheter ablation versus 29% in patients who have received AAD (P = 0.004). (95) Another study, the RAAFT-2, which similarly compared RF ablation and AAD therapy in PAF patients after 2 years, indicated overall higher recurrence rates in both groups, but confirmed the superiority of catheter ablation with a recurrence of 55% as opposed to 72% with AAD treatment (P = 0.016). (81)

Furthermore, it is important to differentiate between *early* and *late AF recurrence*. Early recurrence is defined as an AF episode within 3 months after the procedure, while late recurrence sets in more than 3 months post procedure. Early recurrence falls under the *blanking period* and does not generally imply procedural failure, as the lesion set needs to "mature" during this time. If there is late recurrence, repeat ablation and/or AAD treatment can be taken into consideration. (76)

Unfortunately, there is few data available on the long-term outcome. The first long-term trial included 264 patients who were arrhythmia free and not receiving AAD after 12 months following catheter ablation with PVI. The mean follow-up time amounted to 28 months with a variation of ± 12 months. Overall, 23 of these patients (8,7%) had an AF relapse, while among those who conducted a 5-year follow-up the recurrence rate was 25.5%. But what factors are responsible for an earlier recurrence in some AF patients? One systematic review compared a large number of trials and found no reliable and consistent predictors of earlier recurrence. (96) Nevertheless, more persistent forms of AF (stronger effect with longer duration) and several concomitant conditions such as older age, obesity, sleep apnea, hypertension, increased LA size and LA fibrosis seem to have a negative impact on the outcome of catheter ablation as some studies have shown. (76)

Lastly, there is overwhelming evidence that permanent PVI is rarely achieved in a single procedure, with reconnections of at least one PV in around 80% or more of patients and thus requiring additional therapy. This might be an explanation on improved success rates after 2 or more procedures and/or AAD treatment compared to a stand-alone single procedure. (76)

Complications

Though catheter ablation is a complicated and delicate procedure by nature, it is regarded as safe and associated with a low risk of complications, when performed by an experienced electrophysiologist in a specialized center. One study analyzed the occurrence of complications with catheter ablation in the United States between 2000 and 2010: The overall rate of complications amounted to 6.29%; cardiac complications were most common with 2.54% next to vascular complications (1.53%), respiratory complications with (1.3%) and neurological complications (1.02%). There was also a significant correlation between the frequency of complications and few operator (<25 procedures) and hospital volume (<50 procedures) numbers. (97) A summary of frequent complications associated with catheter ablation is given in Table 9.

Complication	Incidence
Asymptomatic cerebral emboli	2-15%
Cardiac tamponade	0.2-5%
Stroke and TIA	0-2%
Air embolism	<1%
Pulmonary vein stenosis	<1%
Death	<0.1-0.4%
Phrenic nerve palsy	0-0.4%
Atrial esophageal fistula	0.02-0.11%

Table 9: Complications occuring with catheter ablation arranged by frequency. (76)

1.2 Heart failure (HF)

1.2.1 Definition

Heart Failure is a chronic condition involving symptoms such as general fatigue, shortness of breath after brief distances of walking or even rest. On clinical examination patients present with signs of volume overload (e.g. jugular vein distention, peripheral and/or pulmonary edema). Though the term "heart failure" involves both ventricles, it usually refers to left-sided heart failure. According to the 2016 ESC guidelines, the diagnosis heart failure is only applicable in symptomatic patients. An early form, which solely presents itself with an altered cardiac function and showing no symptoms, is called systolic or diastolic left ventricular dysfunction, depending on the form of dysfunction (see section 1.1.3 pathophysiology). The term "congestive heart failure" refers to patients with signs of volume overload. (98) Acute HF describes the sudden occurrence or worsening of typical signs and symptoms within 24 hours and can arise from an ongoing chronic HF, which is referred to as "acute decompensation", or a previously healthy patient. (99)

There are different forms of HF defined through the left ventricular ejection fraction (LVEF) (see also Table 10): An LVEF ≥50% is considered normal (Heart Failure with preserved Ejection Fraction, HFpEF), while the recently introduced HF with mid-range EF (HFmrEF) spans from 40-49%. Lastly, patients with HF and reduced EF of <40% form the third group (HFrEF). EF, among other metrics involving heart function, is typically measured through transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE). Echocardiography in general is the best tool for the initial diagnosis of heart failure if there is reasonable suspicion (above mentioned signs and symptoms, any ECG abnormalities, cardiovascular comorbidities). (65-74) Natriuretic peptides (NT-proBNP or BNP) are elevated with heart failure and can help identify patients who should undergo echocardiography. (98)

For the assessment of HF patients' capacity for exercise and therefore the progression of HF, the NYHA (New York Heart Association) classification system is a validated tool, which has been widely used. Table 11 describes the four different NYHA classes, which range from asymptomatic at class 1 to severe symptoms at rest in class 4. It is important to note that although symptom severity correlates with survival in HF, well-adjusted patients in a low NYHA class might still have a considerable risk of hospitalization and death. (98, 100)

Form of HF	EF range
HFpEF (HF with preserved EF)	≥50%
HFmrEF (HF with mid-range EF)	40-49%
HFrEF (HF with reduced EF)	<40%

Table 10: Forms of HF and corresponding LVEF. (98)

NYHA class	Description
I	Patients have cardiac dysfunction, but ordinary exercise does not cause any symptoms.
II	Patients have cardiac dysfunction, ordinary exercise causes symptoms such as dyspnea and fatigue. (eg. walking multiple staircases)
III	Patients have cardiac dysfunction, less than ordinary exercise causes symptoms such as dyspnea and fatigue. (eg. short distances of walking on level ground)
IV	Patients have cardiac dysfunction and show symptoms such as dyspnea and fatigue at rest. Any additional exercise increases the severity of the symptoms.

Table 11: New York Heart Association (NYHA) classification system. (100)

1.2.2 Epidemiology

Heart Failure is one of the most common cardiovascular diseases with an overall prevalence around 1-2% in developed countries. It is mostly a disease of the elderly, as it practically does not occur in patients aged <50 years. Above 50 years however, prevalence and incidence rates gradually rise with increasing age: in the 2006 analysis from the Rotterdam study, the prevalence of HF was 1% among 55-64 years and over 10% in those aged 85 years and older. The same is true for incidence, which was calculated at 2.5/1000 person years for the age group 55-64 years and 44/1000 person years for 85 years and older respectively. (99) In addition, a more recent publication reported a decline over the years in overall incidence and an increase in prevalence of HF among all age groups. Two groups based from data in

Sweden were compared in this study, the first dating from 2005-2013 and the second 2010-2015. The authors commented this trend might be due to patients with HF surviving over longer periods of time. (101)

Though therapeutic management has improved greatly over the years, patients with HF are still hospitalized frequently and life expectancy is reduced. Another analysis based on the Rotterdam study evaluated survival rates based on prevalent and incident HF. The calculations based on incident cases allowed to include newly occurring (acute) HF and presented the following differences: After 1, 2 and 5 years survival probability based on prevalence was 89%, 79% and 59%, while the analysis based on incidence yielded lower survival rates at 63%, 51% and 35% respectively. These findings confirm data from the Framingham study, where after an initial 30-day mortality of around 10-20% upon onset of HF long term survival was more gradual. Furthermore, several studies have confirmed sudden cardiac death in up to half of the cases as the main cause of death among HF patients, followed by progressive heart failure as the second most common. (99)

1.2.3 Pathophysiology

Heart failure is typically caused by a complex interaction of several concomitant clinical syndromes, which center around three pathophysiological mechanisms: impairing contractility, increasing afterload and impairing diastolic filling of the ventricles. Furthermore, the term *systolic dysfunction* refers to HF with an underlying impairment of ventricle contractility or increased afterload leading to reduced systolic emptying of the ventricle. On the other hand, diastolic dysfunction is used in the context of abnormalities regarding diastolic relaxation and diastolic filling of the ventricle. HF patients have earlier been categorized according to the pathophysiological mechanism in one of these groups, an exact differentiation was not always possible though. Hence it is much more feasible to use a classification involving EF. (102)

As a result of reduced cardiac output, certain compensatory mechanisms are activated: The Frank-Starling mechanism is triggered due to increased ventricle pressure and stretching of myocardial fibers, counterbalancing the loss in stroke volume. Sympathetic activation entails an elevated heart rate and improvement in contractility, while the engagement of the renin-angiotensin-aldosterone system leads to an increase in peripheral vascular resistance and intravascular volume. These effects may initially have a positive impact on heart function but worsen the condition even further in the long run. (102)

Depending on the etiology, HF may have a sudden onset with dramatic progression in the form of acute heart failure or manifest over several years as chronic HF. A number of diseases have been identified to predispose HF: Coronary artery disease (CAD), which leads to ischemic cardiomyopathy, valvular diseases including mitral and aortic regurgitation and dilated cardiomyopathy are common causes of systolic dysfunction. Arterial Hypertension and severe aortic stenosis maintain constant pressure overload, while left ventricular hypertrophy and restrictive cardiomyopathy impair diastolic filling, all four of which predispose diastolic dysfunction. (102)

Certain cardiomyopathies known to cause HF can also predispose AF and are therefore discussed separately in the following:

Ischemic Cardiomyopathy (ICMP)

The underlying cause of ICMP is a mismatch of oxygen supply and demand in the myocardium. It most commonly occurs as a consequence of CAD (sometimes even used synonymously with ICMP), as coronary blood flow is severely reduced. The resulting ischemia leads to accumulation of metabolic waste as well as insufficient ATP production and myocytes switching to anaerobic pathways. As a consequence, contraction and relaxation of the heart are impaired, since they are both energy dependent processes. In addition, the increased amount of metabolic waste seems also to predispose the occurrence of arrhythmias such as AF. (102)

In the context of ischemia and its effect on the contractile function of the myocardium two terms are commonly used: *myocardial stunning* describes the systolic dysfunction of myocytes shortly after temporary acute ischemia. In this condition, the myocardium recovers fully over time. *Myocardial hibernation* on the other hand features gradually progressing systolic dysfunction in chronic heart failure and is irreversible once necrosis occurs, even after normal blood flow is restored. (102)

Dilated Cardiomyopathy (DCMP)

DCMP refers to an enlargement of the heart chambers. Usually all four chambers are affected, but dilatation may also happen in one side of the heart only. A range of conditions have been identified to cause DCMP, among which are inflammatory causes (viral infections, sarcoidosis), toxic (alcoholism, chemotherapy), metabolic (hypothyroidism, hypocalcemia, hypophosphatemia) and neuromuscular (muscular dystrophy). A good portion of DCMP cases have also been linked to certain genetic mutations. (102)

Dilatation of the heart wall and loss of myocytes lead to an impaired contractility and consequent reduction in stroke volume and cardiac output. DCMP also conveys a certain risk for AF through dilatation of the atria. (102)

Tachycardia-induced Myopathy (TIC)

TIC is a cardiomyopathy precipitated by prolonged and recurring tachycardia. AF has been identified as the most common cause, though multiple other arrhythmias such as supraventricular and ventricular tachycardia have been associated with TIC as well. Repeated rapid pacing in animal models was predisposing of progressive HF with similar structural changes and pathophysiological mechanisms to DCMP, these included a loss of myocytes with a reduction in myocardial contractility and cardiac output, dilatation of the left ventricle and higher than normal filling pressures. Compensatory mechanisms generally occurring with HF and further leading to a downward spiral in disease progression have also been observed. The mentioned changes were reversible in most of the animal models after treatment of the associated arrhythmia, which has also been confirmed by other studies in humans. (103)

1.2.4 Management and therapy

1.2.4.1 Risk factor management

There is notable evidence HF can be prevented through the management of modifiable risk factors. Arterial hypertension, diabetes, smoking and dyslipidemia are predisposing of CAD and associated HF. (104) For example, considerable risk reduction can be achieved in subjects aged 75 years or older by lowering blood pressure to <140 mmHg systolic, with an even greater effect if <120 mmHg (I A recommendation). (98, 105) Similarly, sodiumglucose cotransporter type 2 (SGLT-2) inhibitors have been found to reduce major cardiovascular events in patients with type 2 diabetes. Though the mechanisms of these relatively new drugs are not fully understood as of now, there might be a direct protective effect of the myocardium, vessels and kidneys apart from their antidiabetic effects. (106) There is no clear evidence of risk reduction after ceasing nicotine use, but as epidemiological studies have shown certain associations it is reasonable to instruct patients in doing so. Lastly, statins as a means of lowering lipid levels are recommended in subjects with or at high-risk of CAD (I A recommendation). (98)

1.2.4.2 HF specific therapy

HFpEF vs. HFrEF

The following treatment options are largely exclusive for use in patients with HF and reduced EF as the observed effects in such patients could not be reproduced in HF with mid-range or preserved EF. The ESC guidelines recommend to primarily treat concomitant cardiovascular diseases in such patients (I C recommendation) and relieve hypervolemia with diuretics in order to improve symptoms of the same (I B recommendation). (98)

Drug therapy

Angiotensin converting enzyme (ACE) – inhibitors and beta-blockers are the foundation of the pharmacological therapy in HFrEF, as studies have shown a significant reduction of the hospitalization rate as well as mortality with these drugs compared to placebo. The ESC recommends combining an ACE – inhibitor and beta-blocker in all symptomatic HF patients with reduced EF (I A recommendation). If subjects remain symptomatic under this therapy, a mineralocorticoid receptor antagonist (MRA) should be introduced (I A recommendation), as a similar effect on risk of hospitalization and death has been reported in such patients. In the next step, this triple therapy might also be replaced with the combination drug sacubitril/valsartan in symptomatic patients despite optimal treatment (I A recommendation), as an even lower hospitalization and mortality rate has been reported. With diuretics, no effects on the prognosis of HF have been reported to date. Use of these drugs is therefore only indicated to counteract signs and symptoms of congestion and they should be kept at the minimum required dose (I A recommendation). (98)

Device therapy

Device therapy is beneficial in HFrEF patients with certain comorbidities. An implantable cardioverter-defibrillator (ICD) is effective in preventing sudden cardiac death and indicated when there is risk on the occurrence of bradycardia or ventricular arrhythmias (I A recommendation). It is noteworthy that an ICD should not be implanted within 40 days after acute myocardial infarction, as it does not have protective effect at this time (III A recommendation). Cardiac resynchronization therapy (CRT) on the other hand, improves ventricular function, symptoms and mortality in patients with HFrEF and left bundle branch block (LBBB). CRT is recommended with QRS duration ≥130 ms and typical ECG morphology (varying evidence: I A recommendation for QRS ≥150 ms, I B for QRS 130-149 ms). However, QRS <130 ms is a contraindication (III A recommendation). (98)

Heart transplantation and mechanical circulatory support

Patients with acute heart failure or end-stage HFrEF are eligible for heart transplantation when all other treatment options fail and there is no chance of recovery. There have been no randomized trials on its effectiveness, but it is a generally accepted therapy for the given indication. Donor hearts are scarcely available though and transplantation cannot always be performed. Left ventricular assist devices (LVAD), extracorporeal life support (ECLS) and extracorporeal membrane oxygenation (ECMO) can be utilized as a means of mechanical circulatory support in patients with terminal HF, who cannot be stabilized otherwise. These devices maintain heart function either until recovery (termed bridge to recovery), a heart transplant is available (“bridge to transplantation”) or permanently as an alternative to heart transplantation (“destination therapy”). (98)

1.3 Atrial fibrillation and Heart Failure

1.3.1 Pathophysiology

AF is prevalent in more than half of HF patients, while there were more than one third of AF patients with HF. (107) With similar risk factors such as hypertension, diabetes, smoking and coronary artery disease as well as shared pathophysiological mechanisms AF is predisposing of HF as well as the other way around. One main process with HF is the activation of the renin-angiotensin-aldosterone (RAAS) system, which leads to fluid retention and increased filling pressures in the myocardium. Atrial dilation and fibrosis are a result thereof, which in turn entail the occurrence and progression of AF through reentry and focal ectopic activity, two mechanisms common with this arrhythmia. An altered Ca^{2+} channel function has also been observed in HF patients, leading to the formation of early and delayed afterdepolarizations. On the other hand, irregular atrial firing impairs left ventricular filling and therefore results in a decreased cardiac output. Furthermore, fast ventricular pacing in AF is associated with tachycardia-induced cardiomyopathy and can further comprise LV function. Since AF and HF are progressive, chronic diseases the common pathophysiology causes a vicious circle with increasing severity in both conditions over time. (2, 108)

Studies have shown that incident AF in preexisting HF has a worse prognosis with higher mortality than the other way around. (2, 3) HF patients generally show higher morbidity than AF patients, which might be one explanation for this observation. (98)

1.3.2 CASTLE-AF

The Catheter Ablation for Atrial Fibrillation with Heart Failure (CASTLE-AF) study investigated the outcome of patients with HFrEF after AF catheter ablation compared with antiarrhythmic drug therapy. It was a joint trial between several specialist centers for electrophysiology and published in the New England Journal of Medicine. (6)

Methods. CASTLE-AF was conducted as a randomized, open-label, controlled trial. Patients with paroxysmal or persistent AF as well as heart failure with LVEF ≤35 % were included in the study. PVI was performed in those who received catheter ablation. The primary study endpoints were hospitalization precipitated by HF progression or death from any cause. (6)

Results. A total of 363 patients was included in the statistical analysis, of which 179 underwent catheter ablation and 184 received medical therapy. The primary endpoints occurred in significantly fewer patients who underwent catheter ablation compared to ones who received medical therapy (51 patients or 28.5% compared to 82 patients or 44.6%; P = 0.006). Furthermore, the LVEF increased 8.0% with catheter ablation as opposed to 0.2% (P = 0.005) with medical therapy at the 60-month follow-up. (6)

Discussion. The authors concluded that catheter ablation showed a better outcome in patients with paroxysmal or persistent AF and HFrEF regarding mortality and hospitalization rate. These results are consistent with several other trials such as the CAMTAF (Catheter Ablation versus Medical Treatment of AF in Heart Failure) trial (109), further undermining the effectiveness of AF catheter ablation in patients with HFrEF. The authors also pointed out the limitations of the study, which were the lack of blinding regarding randomization and treatment as well as the existence of ICD or CRT-D in all patients that might have affected mortality in both groups. (6)

2 Methods

A single-center, retrospective study at the University Hospital of Graz was conducted to compare the long-term outcome of AF catheter ablation in patients with heart failure and preserved systolic function versus heart failure and reduced systolic function. For this reason, adult AF patients with or without concomitant HF, who underwent their first catheter ablation from 2011 until 2018, were included in the analysis.

Patients were assigned to one of two groups according to the left ventricular ejection fraction (LVEF), which was assessed by means of echocardiography (mostly transesophageal, in rare cases also transthoracic) preceding the catheter ablation procedure. Normal systolic function was defined as LVEF ≥55% (nEF cohort), while a LVEF <55% was regarded as reduced systolic function (rEF cohort).

The main endpoint was AF recurrence after catheter ablation, which was defined as an episode of AF documented by 12-lead ECG lasting at least 30 seconds or the occurrence of typical symptoms for AF. Recurrence was actively monitored by means of 24-hour Holter ECG and assessment of patient symptoms at a 3- and 12-month follow-up after the procedure. Successful outcome was defined as AF and atrial tachycardia free survival during follow-up starting 3 months after the procedure. Any arrhythmia occurring within the 3-month blanking period after catheter ablation was disregarded.

2.1 Database

Data for this study was collected retrospectively in a web-based database. For this purpose, patient files and documents were accessed using the hospital information system openMEDOCS (open Medical and nursing Documentation and Communication network of Styria). These included the ablation procedure protocol, nursing documentation, echocardiography report, discharge letter and reports from out of hospital specialists.

Several patient characteristics were registered in the database, beginning with age, gender, height and weight. In the following, cardiovascular comorbidities, the CHA_2DS_2-VASc and HAS-BLED scores as well as use of antiarrhythmic drug therapy and oral anticoagulation were recorded. Using the echocardiography report, a number of heart metrics such as the left ventricular systolic function and the diameter of the left and right atria were included. Regarding the ablation procedure, type and duration of AF, indication for the procedure, mapping system, type of ablation and used catheter, heart rhythm during the procedure and complications were registered.

Furthermore, specialist reports were used to document outcome at 3- and 12-month follow up as well as any findings and recurrence beyond this period for patients who remained arrythmia-free.

2.2 Statistical analysis

The statistical analysis was carried out using IBM® SPSS® Statistics version 23.0.
Study groups were compared based on an intention-to-treat approach. There was a differentiation between single and multiple procedure success. Patients diagnosed with PAF and concomitant HF of any type, who underwent catheter ablation, were included in the study. Patients who had persistent forms of AF, previous catheter ablation procedure before 2011 or did not receive oral anticoagulation following catheter ablation were excluded from analysis.

Qualitative variables are depicted either by percentage or count and were compared using the chi-square test. Quantitative variables are represented as means with standard deviation (+/- SD), by median and interquartile range, the comparison was made through the utilization of the Mann-Whitney U test. Continuous variables, given the fact they were normally distributed, were tested for significance between both groups by use of the T-Test, otherwise the Wilcoxon signed-rank test was used. Statistical significance was assumed, if a two-sided P value was less than 0.05. The outcome was analyzed by measuring the time-to-first-event, which was tested for significance by means of log rank test and is described by Kaplan-Meier estimators.

3 Results

3.1 Baseline characteristics

446 patients underwent catheter ablation and were included in the AF registry from 2011 until 2018. 274 of those patients met the inclusion criteria for this study. 243 patients had normal left ventricular function (EF 64±5%, nEF), while 31 patients had reduced left ventricular function (EF 49±10%, rEF).

The cohorts were comparable regarding baseline characteristics (see table 12). The only statistically significant difference was found in left atrial diameter, where the rEF group had significantly more pronounced atrial dilatation.

Variable	nEF (n=243)	rEF (n=31)	P-value
Systolic function (EF)	64±5%	49±10%	-
Female patients	26%	19%	P=0.29
under AAD treatment	42%	58%	P=0.12
Age (years)	56 (±12)	60 (±12)	P=0.12
BMI	27 (±5)	29 (±4)	p=0.08
Arterial Hypertension	54%	52%	P=0.15
Diabetes	4%	7%	P=0.26
Prior stroke	4%	3%	P=0.38
CHA_2DS_2-VASc	1 [0,2]	1 [0,2]	P=0.8
HAS-BLED Score	1 [0,2]	1 [1,2]	P=0.56
LA size (mm)	51±7	56±7	**P=0.002**
Follow-up duration (days)	340 [122, 555]	192 [107, 452]	P=0.12

Table 12: Patient baseline characteristics.

3.2 Ablation techniques

The most common ablation techniques performed in the catheter ablation procedures were pulmonary vein isolation and cavotricuspid isthmus (see table 13). In some cases roof lines were applied as well. Mitral isthmus line was applied in 6 nEF patients, but in none of the rEF group. Radiofrequency ablation was predominantly used in both cohorts, while the remaining patients were treated with cryoballoon catheters.

Ablation lines	nEF (n=243)	rEF (n=31)	P-value
Pulmonary vein isolation (PVI)	98,8%	96,8%	P=0.31
Cavotricuspid isthmus (CTI)	21%	20%	P=0.19
Roof lines	2.5%	3.2%	P=0.4
Mitral isthmus ablation	3%	-	-
Ablation technique			
Radiofrequency	96%	90%	P=0.13

Table 13: Ablation lines and techniques applied during procedures.

3.3 Outcome

The outcome of catheter ablation was examined for both groups in regard to single and multiple procedure success. 47 nEF patients (19%) and 7 rEF patients (23%) in rEF required more than one procedure to achieve freedom of AF (P=0.17). 17% in nEF and 19% in rEF underwent 2 procedures in total, while more than 2 catheter ablations were performed in 2% nEF vs. 3.2% rEF.

There was no statistically significant difference as calculated by log rank test in regard to the single procedure success rate after end of follow-up (see Figure 3 and Figure 4). The success rate improved after multiple procedures, showing a slightly better outcome in the nEF cohort (figure 3).

At the end of follow-up, 58% of nEF patients as opposed to 65% of rEF patients were still receiving antiarrhythmic drug treatment (P=0.12).

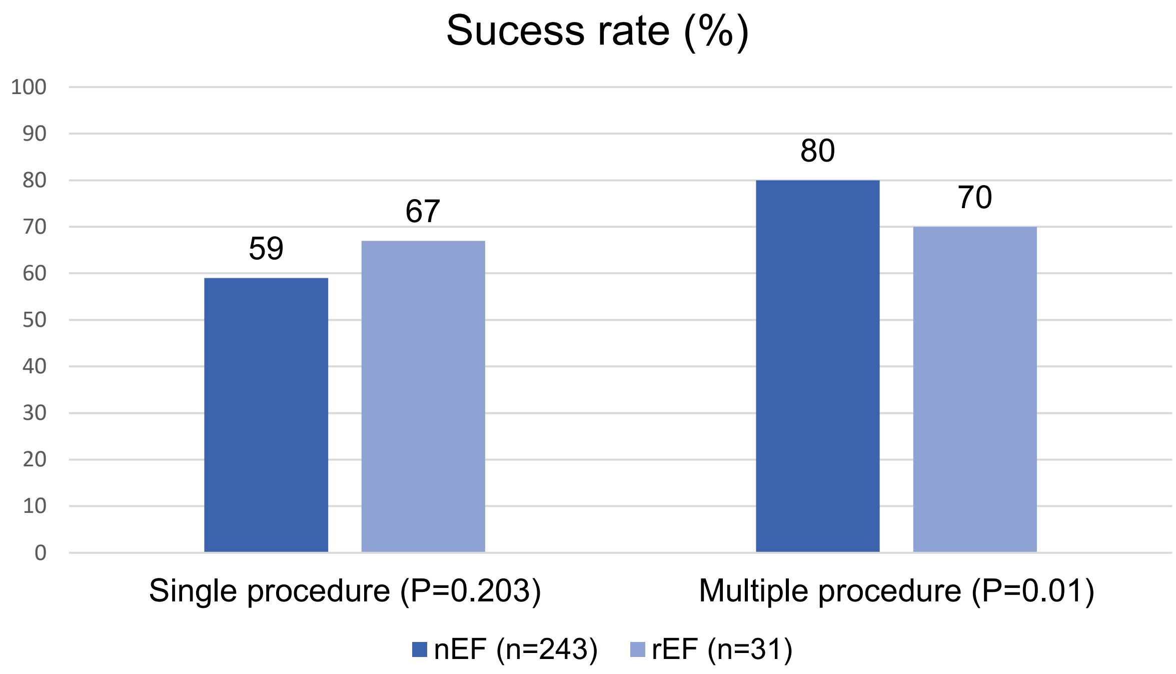

Figure 3: Single and multiple procedure success rates in nEF vs. rEF patients.

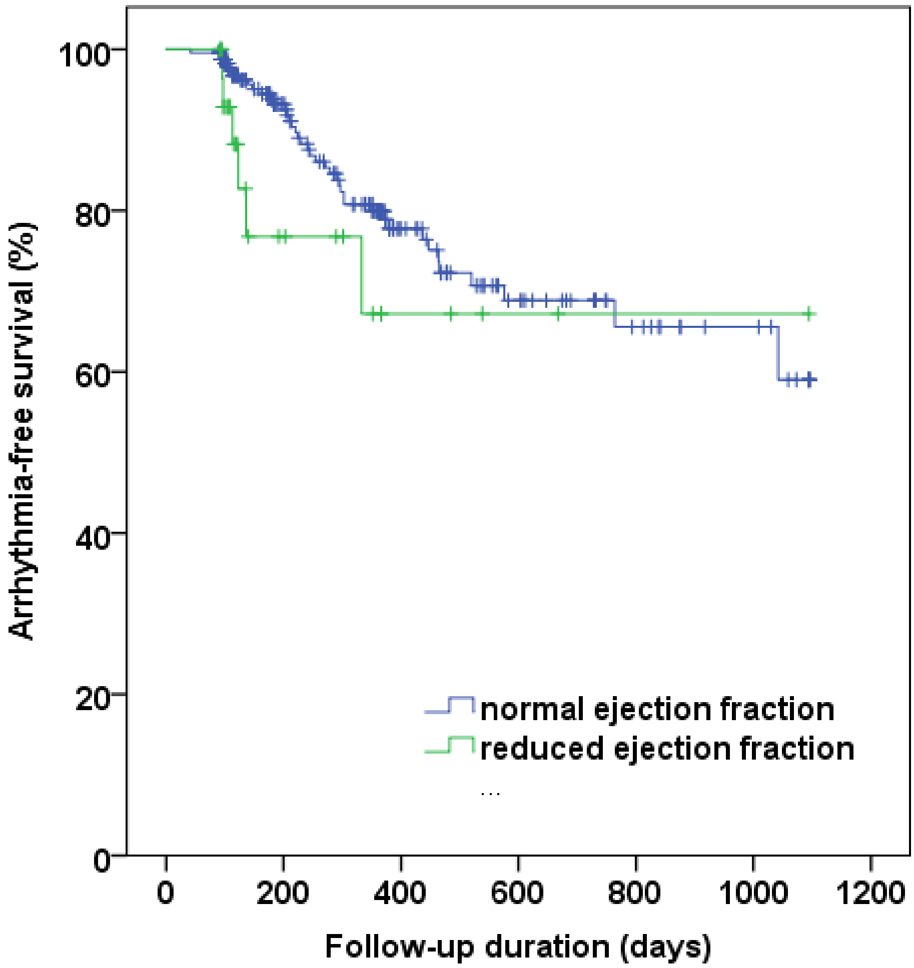

Figure 4: Single procedure arrhythmia-free survival in nEF vs. rEF patients.

3.4 Complications

Overall, complication rate was low (inguinal aneurysm in 1 nEF patient, 0.4%). Cardioversion had to be performed before demission from the ward in some cases, while 2 nEF patients had signs and symptoms during their hospital stay related to catheter ablation (perimyocardial irritation; stabbing chest pain during breathing). Ablation was repeated in about every fifth patient.

	nEF (n=243)	rEF (n=31)	P-value
Cardioversion before demission	4%	7%	P=0.25
Repeat ablation	19%	23%	P=0.17

Table 14: Complications after catheter ablation of nEF vs. rEF patients.

4 Discussion

In this retrospective analysis of AF patients undergoing catheter ablation in Graz, we found out that there was no statistically significant difference regarding the single procedure success rate with normal ejection fraction compared to reduced ejection fraction. After multiple procedures there was an increase in success rate in both cohorts, though slightly favoring patients with normal ejection fraction. The complication rate was overall low and comparable between both groups.

4.1 Clinical Relevance

Atrial fibrillation and heart failure frequently coexist and share pathophysiological mechanisms such as atrial remodeling. Additional AF in patients with HF and reduced ejection fraction causes an increase in mortality. Thus, restoring sinus rhythm in such patients can lead to an improved left ventricular contraction and quality of life. Nevertheless, some studies have found no mortality benefit for employing a rhythm control strategy in this context. (4, 5) In contrast, rhythm control is generally regarded as equally efficient to rate control, with catheter ablation being an established rhythm control therapy.

Several studies have investigated the use of ablation procedures in patients with HF, though only few prospective, randomized trials have been conducted. CASTLE-AF examined long-term outcome of catheter ablation vs. antiarrhythmic drug treatment in patients with paroxysmal as well as persistent AF and concomitant HFrEF. The trial found that catheter ablation is superior to medical therapy and improved the mortality rate. (6) Furthermore, PABA-CHF (Pulmonary Vein Antrum Isolation versus AV Node Ablation with Bi-Ventricular Pacing for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure) reported superiority of catheter ablation over atrioventricular-node ablation with biventricular pacing in patients with concomitant HF (110), while AATAC (Ablation versus Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD) showed that catheter ablation is also superior to amiodarone for the treatment of persistent AF and HF (111). Additionally, one meta-analysis, which compared data from PABA-CHF and 3 more randomized trials, concluded that catheter ablation improved LVEF, quality of life and functional capacity significantly better than rate control strategies in patients with AF and HF. (112)

It is also important to note that ablation has to be performed in specialist centers (>50 procedures annually) by experienced electrophysiologists (>25 procedures annually) to minimize risk of complications and achieve comparable outcome as stated in recent literature. (76)

The above described results from several randomized trials were consistent with findings from the underlying study for this thesis. Consequently, there is considerable evidence that catheter ablation is suited and reasonable for clinical use in patients with AF and HFrEF.

4.2 Limitations

As opposed to before mentioned randomized trials, this study presents a retrospective analysis based on a patient register. Therefore, patient cohorts might be uneven and possible confounders not factored in. Although patient files were thoroughly scrutinized, certain missing data is possible. Additionally, the single-center setting and low percentage of women and number of patients in general might not be representative and results may vary in a larger population.

There was an uneven number of patients regarding the study cohorts, with the rEF population being underrepresented. Furthermore, there was a considerable variation in systolic function in the rEF cohort, which was larger than the variation in nEF. Though PVI was intended to be performed in all AF patients, there were some cases, where the procedure was aborted because no AF could be detected. Due to the intention to treat analysis, the rate of PVI was slightly under 100%.

In summary, more multi-center, randomized, prospective trials are needed to investigate catheter ablation in an underrepresented patient selection. Additionally, study cohorts should be predefined and homogenous.

5 Conclusion

In patients with concomitant HF undergoing AF catheter ablation there was no significant difference in outcome with normal ejection fraction as opposed to reduced ejection fraction. The complication rate was also comparable between both cohorts. Thus, it can be concluded that catheter ablation is efficient and safe for the treatment of AF in patients with reduced systolic function.

The occurrence of cardiovascular diseases including AF and HF is increasing with the general ageing of the population. Therefore, it is of utmost importance not only to reevaluate established therapy options and compare them to newly available ones but to also investigate those in certain patient groups and combinations of conditions.

Several clinical aspects on both mentioned diseases were covered in the first part of this thesis. In the second part, an outline on patient characteristics and the outcome and complication rate of catheter ablation at the University Hospital Graz was given. The data from this can be used for reviews and international comparisons to provide more representative evidence and give well-founded recommendations on treatment of certain patient populations.

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