Diploma thesis

The impact of arterial hypertension on atrial fibrillation and recent evidence-based therapy

Arterial hypertension as most important risk-factor for development and perpetuation of atrial fibrillation

Submitted by

Dominik Jenny

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Medical University Graz

conducted by the

University Clinic for Internal Medicine

Department of Cardiology

supervised by

Univ.-Prof. Priv.-Doz. Dr.med.univ. Daniel Scherr

Dr.med.univ. Ursula Rohrer

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Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used.

Lauterach, 13.06.2022 Dominik Jenny eh.

Acknowledgement

At this point I would like to thank all those who supported and motivated me during my medical studies and in the preparation of this thesis.

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Abbreviations

ACEi	Angiotensin-converting enzyme inhibitor
AERP	Atrial effective refractory period
AF	Atrial fibrillation
AFL	Atrial flutter
AFL	Atrial flutter
AHT	Arterial hypertension
AP	Action potential
APD	Action potential duration
ARB	Angiotensin receptor blocker
BP	Blood pressure
CA	Catheter ablation
cAF	Chronic atrial fibrillation
CCB	Calcium channel blocker
CHF	Chronic heart failure
CI	Confidence interval
CIED	Cardiac implanted electronic device
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
CV	Cardioversion
CVD	Cardiovascular disease
DAD	Delayed afterdepolarization
DM	Diabetes mellitus
DOCA	Deoxycorticosterone acetate
EAD	Early afterdepolarization
ECG	Electrocardiogram
EF	Ejection fraction
EHRA	European Heart Rhythm Association
ESC	European Society of Cardiology
ESH	European Society of Hypertension
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction

HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
HRQoL	Health-related quality of life
HT	Hypertension
LA	Left atrium
LV	Left ventricle
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NDCC	Non-dihydropyridine calcium channel blocker
NSAID	Non-steroidal anti-inflammatory drug
OAC	Oral anticoagulation
pAF	Paroxysmal atrial fibrillation
PV	Pulmonary veins
RAAS	Renin angiotensin aldosterone system
RAP	Rapid atrial pacing
RCT	Randomized controlled trial
SCORE	Systematic Coronary Risk Evaluation

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Zusammenfassung

Hintergrund: Aufgrund besserer medizinischer Versorgung erreicht die Bevölkerung zunehmend ein höheres Lebensalter. Dies wirkt sich insbesondere auf die Prävalenz von Vorhofflimmern aus, da dessen Inzidenz mit dem Alter stark zunimmt. Als isolierter Risikofaktor hat arterielle Hypertonie einen starken Einfluss auf die Entstehung und den Verlauf von Vorhofflimmern.

Zielsetzung: Ziel dieser Arbeit ist es, den Einfluss arterieller Hypertonie auf Entstehung und Fortschreiten von Vorhofflimmern im Hinblick auf strukturellen und elektrischen Umbau aufzuzeigen. Zusätzlich soll in der Literatur nach aktuellen und evidenzbasierten therapeutischen Optionen zur Beeinflussung beider Krankheitsbilder gesucht werden.

Methoden: Es wurde eine umfangreiche Literaturrecherche in Pubmed, UptoDate, ClinicalTrials.gov und ScienceDirect durchgeführt.

Ergebnisse: Vorhofdilatation ist ein wichtiges Merkmal des strukturellen Umbaus und kann als Prognosemarker für die Entstehung von Vorhofflimmern verwendet werden. Die Dilatation der Vorhöfe wird zum einen durch Bluthochdruck und zum anderen durch Vorhofflimmern selbst verstärkt ("Vorhofflimmern erzeugt Vorhofflimmern"). Arterielle Hypertonie begünstigt zusätzlich eine verstärkte Fibrose der Vorhöfe. Das elektrische Remodeling führt zu einer Vielzahl von Veränderungen der Ionenkanäle (hauptsächlich davon betroffen sind Ca^{2+}-Ionenkanäle), die schließlich zu einer Verkürzung der effektiven Refraktärzeit der Vorhöfe führen. Diese Veränderungen sind bis zu einem gewissen Grad reversibel, wenn das Vorhofflimmern beendet wird. ACE-Hemmer und AT1-Rezeptorblocker reduzieren die Rate an neu auftretendem Vorhofflimmern im Vergleich zu anderen konventionellen Medikamenten, welche zur Blutdrucksenkung eingesetzt werden. Liegt bereits Vorhofflimmern vor, gibt es einen multimodalen Therapieansatz zur optimalen Behandlung dieser Rhythmusstörung.

Schlussfolgerung: Trotz umfangreicher Forschungsarbeiten in den letzten Jahren ist der genaue Mechanismus der Entstehung und Aufrechterhaltung von Vorhofflimmern, sowie der Einfluss der arteriellen Hypertonie als wichtigster Risikofaktor nach wie vor nicht vollständig geklärt. Weitere Studien müssen durchgeführt werden, um den genauen Mechanismus aufzudecken, damit frühzeitig Behandlungsmaßnahmen ergriffen werden können.

Abstract

Background: Due to better medical care, the population is increasingly reaching a higher age. This has a particular impact on the prevalence of atrial fibrillation as its incidence rises with age. Arterial hypertension as an isolated risk factor has a strong influence on the development and progression of the arrhythmia.

Objective: The aim of this work is to demonstrate the influence of arterial hypertension on the development and progression of atrial fibrillation with special regard to structural and electrical remodeling. In addition, the literature is searched for evidence-based therapeutic options to optimally treat both medical conditions.

Methods: An extensive literature search was performed in Pubmed, UptoDate, ClinicalTrials.gov and ScienceDirect.

Results: Atrial dilatation is an important sign of structural remodeling and can be used as a prognostic marker for the development of atrial fibrillation. Dilatation of the atria is aggravated by hypertension on the one hand and by atrial fibrillation itself on the other ("atrial fibrillation begets atrial fibrillation"). Furthermore, arterial hypertension leads to increased fibrosis of the atria. Electrical remodeling leads to a variety of ion-channel changes (mainly Ca^{2+}-ion channels) which eventually result in a reduction of atrial effective refractory periods. These changes are reversible to some degree as atrial fibrillation is terminated. Angiotensin converting enzymes and angiotensin receptor blockers reduce the rate of new-onset atrial fibrillation compared to other conventional drugs used to lower blood pressure. If atrial fibrillation is already present, a multimodal therapeutic approach is recommended to optimally treat the arrhythmia.

Conclusion: Despite extensive research within the last years the exact mechanism of origin and perpetuation of atrial fibrillation as well as the influence of arterial hypertension as the most important risk factor remain unclear. Further studies need to be done to reveal the exact mechanism so that treatment measures can be taken early.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrythmia in adults and puts a huge burden on affected patients and healthcare system. Between 2% and 4% of the general European population suffer from AF, a 2.5-times rise of prevalence is expected by 2060 due to anticipated longer lifetime.(2) New studies show that in a cohort of European individuals at the age of 55, 1 out of 3 will develop AF in his/her lifetime.(3)

Patients with AF have a higher risk to suffer from stroke, chronic heart failure, myocardial infarction, and systemic thromboembolic events. Also, the psychological well-being is impaired. This increases the morbidity and leads to a higher mortality and higher financial costs for the health care systems. Increasing age, male sex, arterial hypertension, obesity, and obstructive sleep apnoea are known risk factors for atrial fibrillation. Although epidemiologic data show the influence of these risk factors, only little is known about the exact development, progression, and pathophysiology of this arrhythmia.(3, 4)

Arterial hypertension is one of the most important risk factors that provable favours the macro- and microscopic cardiac remodeling as well as electrophysiological changes. In earlier studies, the group of Manninger M. et al could show the influence of arterial hypertension specifically on electrophysiological changes in an animal model of AF and arterial hypertension as an isolated risk factor.(5)

Despite intensive research into the pathophysiological processes of atrial fibrillation, there are still some unexplained gaps in knowledge regarding the development and maintenance of atrial fibrillation. Further research is needed to intervene early and prevent pathological changes in the heart and other secondary diseases.

The first chapter of this diploma thesis addresses epidemiology, diagnostic criteria, clinical symptoms, and risk factors for the development of atrial fibrillation. The most common complications are discussed as well. Furthermore, reference is made to the pathophysiology and current guideline-based therapy.

In the second chapter, the epidemiology and development of hypertension is discussed as well as the used cardiovascular risk assessment. Finally, the treatment according to recent guidelines is presented.

Chapter four addresses the structural and electrical changes in the heart induced by atrial fibrillation with a special attention on the influence of arterial hypertension. Finally, current therapeutic options for hypertension with and without atrial fibrillation are discussed.

1 Atrial fibrillation

1.1 Definition

Atrial fibrillation is an irregularly irregular rhythm with supraventricular origin. It is characterized by low-amplitude baseline oscillations (= f-waves) with a frequency of 300-600 beats/min. These f-waves are very small and can be seen best in lead V1 but can also be invisible. This needs to be differentiated to atrial flutter that might look similar but has a very different arrhythmogenesis. In atrial flutter the so-called “flutter waves” are clearly visible with a rate of 250-350 beats/min., regular and similar in morphology.

The ventricular conduction system is not impaired by AF, resulting in a narrow QRS complex (except pre-existing structural heart changes e.g., bundle branch block, aberrant ventricular conduction). The ventricular rate is often around 100-160 beats/min if untreated.(6, 7)

In AF, the uncoordinated contractions of the atria cause a decrease in their mechanical function, dilatation and stagnation of blood flow, which increases the risk of thrombus formation and therefore thromboembolic events and strokes.(7)

The loss of a coordinated AV-synchronous active atrial contraction is present, leading to decrease in end-diastolic blood volume in the ventricles and subsequently to a lowered cardiac output: a reduction of around 15% (if left heart failure is present even up to 40%).(8)

Because of the irregular R-R interval the diastolic filling time of the ventricles varies a lot resulting in a fluctuation of stroke volume with direct effect on cardiac output.

1.2 Epidemiology

Atrial fibrillation is the most common sustained cardiac arrythmia. Stroke, heart failure and thromboembolic events are just some of the possible secondary complications which can arise from undiagnosed/ untreated AF. The increasing morbidity and mortality of millions of people causes a significant impact on public health burden.(9)

Globally approximately 28.3 million (95% CI 21.5 to 36.2 million) people suffered from AF/ atrial flutter (AFL). Until 2019 these numbers have more than doubled: 59.7 million (95% CI 45.6 to 75.3 million). Of this population 30.3 million were male (95% CI 23.4 to 38.3 million) and 29.4 million were female (95% CI 22.4 to 37.4 million). The prevalence

was 528.72 per 100,000 people (95% CI 401.76 to 675.94) in 1990 and rose to 771.51 (95% CI 591.02 to 973.02) in 2019.(10)

This substantial increase in prevalence can be explained by the progressively increasing age of the population, increased prevalence of risk-factors and better surviving after myocardial infarction.(11)

The following figures present the prevalence of AF/AFL, which were recorded by the Global Health Data Exchange in 2019:

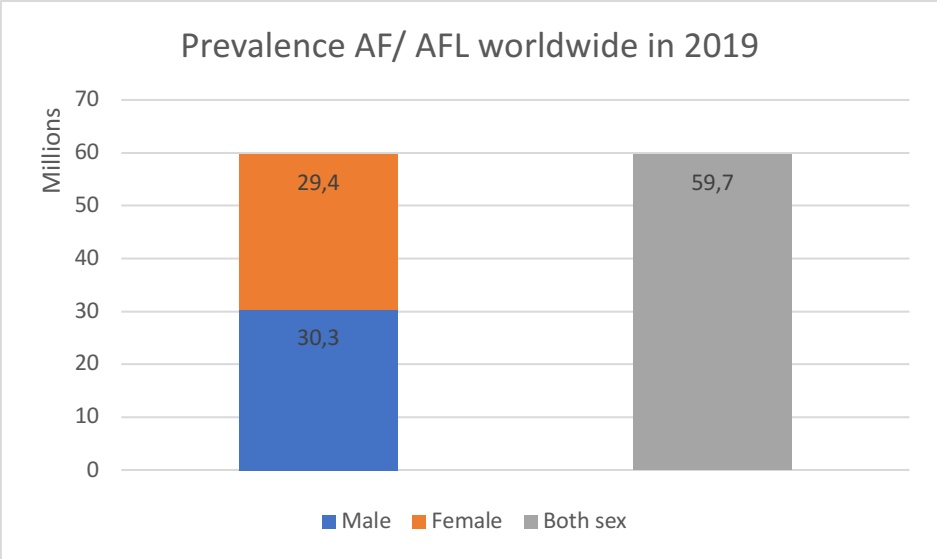

Figure 1: Prevalence AF/AFL globally in 2019(10)

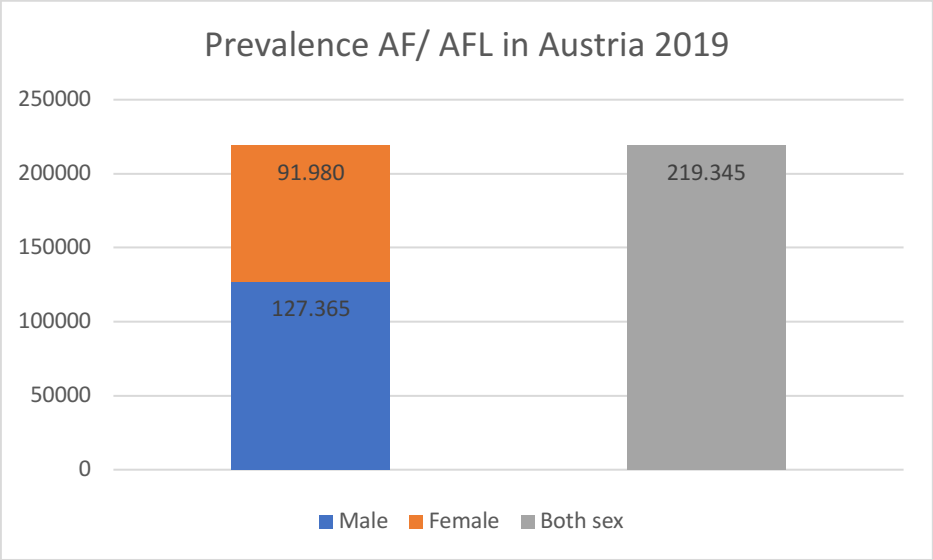

Figure 2: Prevalence AF/AFL in Austria 2019(10)

In 2010 a group of scientists investigated on the prevalence of AF in the European population older than 55 years with a cross-sectional study. Approximately 8.8 million people (95% CI 6.5 – 12.3 million) were affected.

They estimated that this number is going to rise to 17.9 million (95% CI 13.6 – 23.7 million) by 2060 when the prevalence stays stable – this would affect 3,5% of the European population aged 55 years or older. The older the more likely it is to suffer from AF.(2)

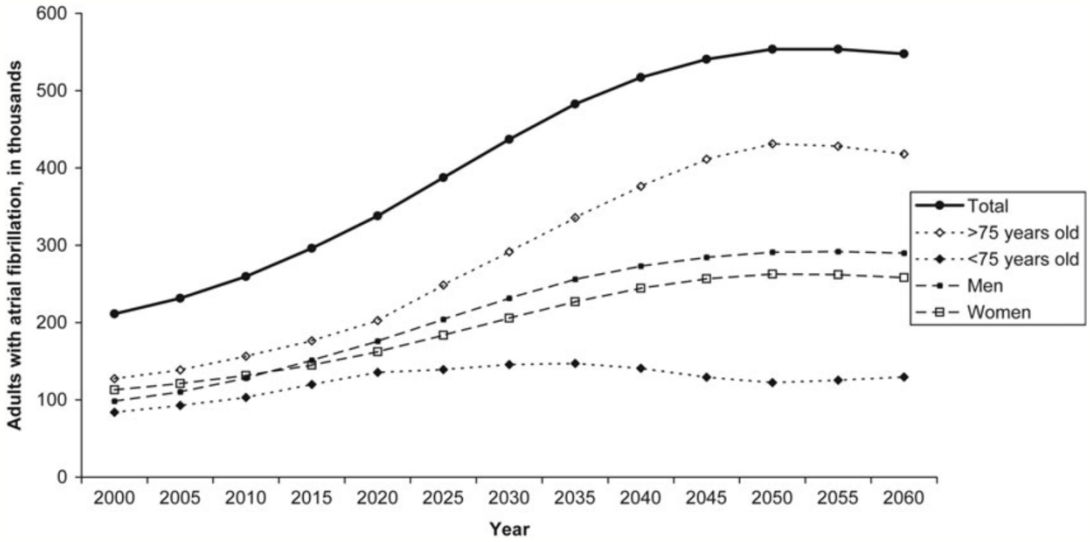

Figure 3: Projected number of adults with AF in the EU between 2000 and 2060(2)

1.3 Diagnostic

1.3.1 Clinical AF

To diagnose AF, it is necessary to record the irregular rhythm with a surface electrocardiogram (ECG). In 2020 the European Society of Cardiology (ESC) updated their guideline: from now on it is possible to diagnose AF either by a full 12-lead ECG or a single-lead ECG tracing of ≥ 30 seconds showing the rhythm abnormality.(3)

1.3.2 Subclinical AF

Cardiac implanted electronic devices (CIEDs) with automated atrial rhythm detection are more and more commonly used, enabling continuous detection of electrical processes in the atria – even if the patient is asymptomatic (absence of palpitations, chest pain, shortness of

breath, diaphoresis, dizziness, loss of consciousness). Therefor new categories of atrial arrhythmia have been established:

Subclinical AF:
Asymptomatic episodes of AF first diagnosed and confirmed by an intracardiac ECG.
Subclinical atrial tachyarrhythmia:
Episodes of AF, AFL or atrial tachycardia recorded by the device without any clinical symptoms.

All of these by CIEDs detected arrythmias should be review and confirmed by a physician to exclude false positives (e.g., far-field signal). The stroke risk needs to be exactly evaluated (e.g., duration of the arrhythmia, age, diabetes mellitus, arterial hypertension, heart failure) to not harm the patients by prescribing anticoagulants. Correct management of these patients is not 100% certain yet.(12)

1.3.3 Smartwatches and fitness bands

Technologies become more and more implemented in our daily life's. Different manufacturers produce smartwatches and fitness bands which can detect the heart rhythm and promise to report arrhythmias like atrial fibrillation and atrial flutter.

One of the biggest studies (The Apple heart study, 2018, USA) enrolled 419,297 people wearing a smartwatch (measuring wrist pulse rate by means of photoplethysmography). 2,161 (0,5%) received an irregular pulse notification. Due to a loss of follow-up 153 (=35% of all evaluated single lead-ECGs) patients were observed with AF confirmed by a single lead-ECG patch.
This was the first large scale study performed on a general public. On the downside the study population was quiet young (average age around 40 years) and it might not be an exact sample of the total population (young people tend to buy newer technologies, high cost of the products, etc.).(13)
Since 2018 the ECG App, in combination with the Apple Watch, is US-FDA (US Food and Drug Administration) cleared (= Class II; not approved!). Yet it is uncertain if smartwatches/ fitness bands can be used for a broad screening of AF in the future or if they contribute to frighten people.

1.3.4 Classification

Atrial fibrillation can be classified by its duration and goal of clinical treatment into 5 subgroups:

First diagnosed: Whenever AF is diagnosed first it should be called "first diagnosed" irrespective of its duration or presence of AF-related symptoms.
Paroxysmal AF: AF that terminates within 7 days of onset (spontaneously or with intervention). Most episodes convert spontaneously back to sinus rhythm within the first 48h.
Persistent AF: AF continuously present for more than 7 days (even if the episode was terminated by an intervention after the 7th day).
Long-standing persistent AF: AF that continuously persists for more than 12 months when decided to adopt a rhythm control strategy.
Permanent AF: Patient and physician accept AF there are no further attempts to restore a sinus rhythm. This rather describes a therapeutic attitude than a pathophysiological attribute.(3, 7)

1.4 Symptoms

Around 50-87% (3) of patients with a new onset of AF are asymptomatic – possible with a worse outcome due to later recognition and treatment. Paroxysmal episodes tend to be more symptomatic whereas recrudescence often stay unrecognised.
Symptoms are variable and their severity can differ from patient to patient: anxiety, palpitation, dizziness, shortness of breath, syncope (due to reduction in cardiac output), polyuria (atrial dilatation leads to an increased release of atrial natriuretic peptide) and pulse deficiency.(8)
Comorbidities (e.g., pre-existing heart failure, chronic obstructive pulmonary disease, anaemia, etc.) can have a negative impact on the symptoms mentioned above and increase the patient's morbidity.

The severity of AF-related symptoms can be classified depending on the patient's daily disability by using the modified European Heart Rhythm Association (EHRA) score.

MODIFIED EHRA SCORE	SYMPTOMS	DESCRIPTION
I	None	AF does not cause any symptoms
2A	Mild	Normal daily activity not affected by symptoms related to AF
2B	Moderate	Normal daily activity not affected by symptoms related to AF, but patient troubled by symptoms
3	Severe	Normal daily activity affected by symptoms related to AF
4	Disabling	Normal daily activity discontinued

Table 1: Evaluation of AF-related symptoms using the modified European Heart Rhythm Association (EHRA) score(3)

1.5 Complications and morbidities

In 1998 the Framingham Heart Study was able to proof that AF poses a greater risk of death in patients aged between 55-74 years than the normal population. The odds-ratio of death with AF was 1.5 (95% CI, 1.2-1.8) for men and 1.9 (95% CI, 1.5-2.2) for women.(14) Up to date several studies support these findings.

Heart failure (HF):

The risk factors for AF and HF are quiet overlapping, 40% of patients with AF will develop HF and vice versa. Patients with AF have a 5-times higher risk to suffer from HF than the normal population.(15) AF is the highest absolute risk increase to suffer from HF compared to all other comorbidities.(16) The incidence of HF with preserved left ventricular ejection fraction (LVEF) (3.3 (95% CI; 3.0-3.7) per 100 person-years) was higher than with reduced EF (2.1 (95% CI; 1.9-2.4) per 100 person-years).(15)

Stroke:

The risk of having a stroke caused by AF is rising with increasing age: at an age of 50 – 59 years AF is causative for stroke in about 1.5%, at an age of 80-89 years in around 23.5%. After the diagnose of AF the risk to suffer from an ischemic stroke rises by 1.5% per year.(15) The outcome of cardioembolic strokes tend to be more severe, fatal, often recurring and with lasting disabilities.(3)

Decreased quality of life:

AF impairs the health-related quality of life (HRQoL) however, exact factors are not known yet. The HRQoL-score of these patients was consistently lower than for healthy persons or patients with any other cardiac disease.(17) A higher EHRA score is associated with a lower QoL and increased rate of hospitalization, but no other major adverse events.(18)

Hospitalizations and costs:

Patients with AF require regularly clinical follow-up (adjusting medication, monitoring anticoagulation, etc) and are twice as likely (37.5%) to be hospitalized than age- and sex-matched control population (17.5%).(15) Tachycardic episodes or acute onset of burden lead to an increased number of emergency room visits. Thus, resulting in higher medical costs than the average person: approximately 2500$/ patient-year.(19)

1.6 Risk-factors

Chronic heart failure (CHF), arterial hypertension, coronary artery disease, structural heart diseases (for example: scars due to myocardial infarction, valvular heart disease), diabetes mellitus and increasing age have a great impact on the development of AF as shown by large cohort studies as the Framingham study.(14, 20)

CHF is the strongest independent risk factor for AF, it is said to be present in 30-40% of affected patients.(20) It leads to a structural and electrical remodeling of the atria and to neurohumoral activation of the Renin-Angiotensin-Aldosterone System (RAAS). CHF and AF have many risk factors in common leading to induction and perpetuation of each other.

Arterial hypertension is the most common comorbidity in patients affected by AF. There is a 1,7-fold risk increase for patients to develop this arrhythmia in comparison to normotensives.(21)

A non-influenceable risk factor is gender: it leads to an 1,5 times greater risk in incidence of AF in men than in women. The risk increases with advanced age in men while this is not the case in women. Furthermore, family history increases the risk of AF, depending on the numbers of suffering parents: if one parent is affected the risk to develop AF rises 1,85 times, if both parents are affected it is 3,17 times.

Apart from non-influenceable factors, especially young patients are affected by AF modifiable risk factors like obesity, obstructive sleep apnoea, cigarette smoking and alcohol consumption. These factors have a huge impact on the development of the arrhythmia. By early intervention the progression can potentially be prevented.(20)

Although intense research has been done over decades, the exact influence and interaction on the development of atrial fibrillation through risk factors is still unclear.

1.7 Pathophysiology

The interaction between trigger and substrate is essential for the initiation and perpetuation of AF. A trigger can be defined as a rapidly firing focus which can initiate the arrhythmia. To sustain the arrhythmia the substrate needs to fulfil certain electrophysiological, mechanical, and anatomical characteristics. Development of this substrate (including electrical and structural atrial remodeling) takes its time which leads from an initially trigger-driven disease to a functional atrial substrate with re-entry mechanisms due to atrial remodeling over time. This is supported by clinical observation that AF often starts as paroxysmal before progressing into a persistent/ permanent state.(22)

Up until now the exact mechanism to keep AF perpetuating are not completely known. Reentry of excitation wavefronts were believed to be the main mechanism for a long time. In 1998 Haissaguerre et al. recognised a focal source of activity located around the origin of the pulmonary veins leading to paroxysmal AF.(23) This discovery drew the attention to "focal" sources.
In the end cellular proarrhythmic mechanism (automaticity or triggered activity) and reentrant mechanism might be responsible in the development of AF - their relative contribution may vary in each patient individually.(1)

1.7.1 Hierarchical and Anarchical Organization

The perpetuation of AF can underly either by hierarchical or anarchical mechanisms:

Hierarchical:

AF is driven by a rapid localized source (e.g., focal discharges and reentrant circuits). The atrial myocardium (also the AV-node) cannot follow the rapid impulses in a 1:1 fashion, resulting in an irregular conduction at a lower rate. Ablating the source of origin will terminate AF in theory, while evidence from randomized-controlled trials to target non pulmonary vein-triggers is still missing and is only done in individual cases.(1)

Anarchical:

Multiple non localized sources act as a driver for AF. The arrhythmia will only be sustained as long as enough sources are present. As ablation of a specific non-localized driver is not possible other strategies to restrict the propagation of wavelets may be successful.(1)

	Hierarchical AF	**Anarchical AF**
Reentrant mechanisms	- Stable mother wave macroreentrant - Stable mother wave microreentrant - Unstable reentrant circuits - Leading circle - Rotor (fixed, wandering)	Multiple wavelets
Cellular proarrhythmic mechanisms (automaticity/ triggered activity)	Automatic foci	Disseminated atrial foci discharges (hypothetical)

Table 2: Examples for hierarchical and anarchical organization of AF(21)

1.7.2 Cellular Proarrhythmic Mechanisms

Enhanced automaticity:

When myocytes with pacemaker activity increase their spontaneous discharge rate, this leads to increased automaticity. This may be due to a reduced action potential threshold (phase 0), a lower resting membrane potential or an increase in spontaneous diastolic depolarisation (phase 4). To date, there is little evidence to support increased automaticity as a proarrhythmic cause of AF.(1)

Abnormal automaticity:

Cells are depolarised by any type of current that reaches the threshold of inward currents. Often the action potential is triggered by Ca^{2+}-inward currents, as the Na^{+}-channels are usually not fully recovered at this point. These automatisms cannot usually be controlled by overdriving, but they are sensitive to drugs that shift the membrane potential into the more negative range (acetylcholine and adenosine).(1)

Triggered activity:

Membrane oscillation following normal action potentials can provoke new action potential if the threshold of depolarizing currents is reached. This can result in self-sustaining runs of triggered activity.(1)

- **Delayed Afterdepolarizations (DADs):**

  DADs occur after a full depolarization of the cell and are favoured by conditions producing a Ca^{2+} overload (e.g., ischemia, ß-adrenergic stimuli, low extracellular potassium, tachycardia). The Ca^{2+} overload in the cell activates the $3Na^{+}$/ Ca^{2+} exchanger which leads, due to an ion-transport, to an inward current I_{Ncx}. Thus, can depolarize the cell.(24)

  Characteristic rate dependence of DADs: the faster the triggering rhythm, the shorter the interval of triggered response, the faster self-sustaining episodes of DADs.(24)

- **Early Afterdepolarizations (EADs):**

  Oscillations that occur during phases 2 or 3 are called early afterdepolarisations. These occur when the activation potential is prolonged by activating "Ca^{2+} window currents". This is when the voltage thresholds for activation and inactivation of Ca^{2+} channels overlap, allowing a rapid change from inactivated to activated state. Another possibility for this is a spontaneous release of Ca^{2+} from the sarcoplasmic reticulum at cytosolic elevated Ca^{2+} concentrations. Most EADs occur during bradycardia, unlike DADs.(1)

1.7.3 Mechanisms of Reentry

- **Circus movement reentry**

  It requires an anatomical structure where the activation can travel along to reactivate previously excited tissue. This tissue needs to be recovered before the next activation arrives. To favour the happening a short refractory period and a low conduction velocity are needed. Because of the excitable gap a wave form outside can block and terminate the reentrant circuit.(1)

Figure 4: Schematic circus movement reentry(1)

- **The leading circle concept**

  In 1973 Allessie et al. proved that an anatomical obstacle is not necessary for a reentrant movement. The wave rotates around a core of tissue that never regains full excitability due to constant electrotonic depolarization. The reentry circuit expands only to the smallest possible loop in which the wave can continue to propagate itself, resulting in an only very small excitable gap. This means external stimuli are less likely to interrupt the reentry circuit (as compared to the circus movement reentry). On the other hand, this arrhythmia is very unstable because small changes in tissue properties, localisation of the circuit and activation cycle length can affect the propagation significantly.(1)

Figure 5: Schematic representation of the leading circle concept(1)

- **Spiral wave reentry**

  The spiral wave reentry theory depends on an equilibrium of “source” (=spreading current of excited tissue) and “sink” (=excitable, downstream cells). If the ratio is shifted too much to one side, propagation will not be possible.

  In concave wavefronts the leading cells activate a littler amount of unpolarized cells, resulting in a high conduction velocity. Whereas in a convex wavefront the source

must activate relatively more downstream cells, leading to a lower conduction velocity.

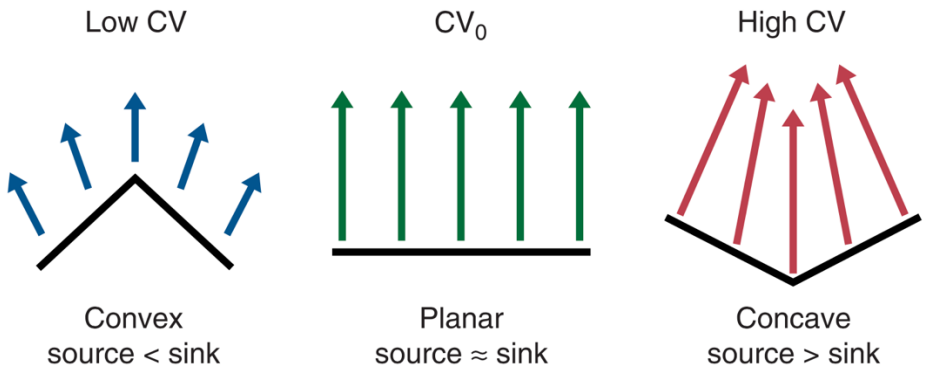

Figure 6: Propagation of wavefronts in spiral wave reentry(1)

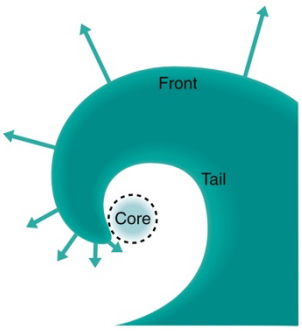

Figure 7: Schematic spiral wave(1)

When a wavefront hits the still refractory tail of another wave perpendicularly, excitation of cells is only possible in newly recovered cells. Thus, creating a wave of the shape of a rotor. The curvature of the wavefront increases towards the core, due to a source-sink mismatch the conduction velocity is at a bare minimum at the core until a block occurs, leaving the core unexcited.

Although spiral wave reentry hasn't been documented in humans, it still provides a thorough explanation for reentry in AF. A possible explanation might be that structural changes (e.g. fibrosis) in the human heart leads to more complex propagation patterns as in many animal models.(1)

- **The multiple wavelet hypothesis**

Since the late 1950s this hypothesis assumes that multiple wavelets wander through an excitable medium in a seemingly chaotic pattern. Multiple wavefront-wavetail interactions lead to wavebreaks and generation of new waves. Blockage, collision, and fusion of these wavelets will lower their number but as long as they won't decrease below a critical amount the arrhythmia will be sustained. Shortening of the

Figure 8: Schematic representation of the multiple wavelet hypothesis(1)

refractory period, slow conduction, heterogeneity of refractoriness and increased tissue mass will increase the likelihood of a stable arrhythmia.(1)

Vaquero et al. believe that local sources are not excluded by the multiple wavelet hypothesis and that stable rotors may even act as source for multiple wavelets.(25)

1.8 Therapy

The ESC guideline on the Management of AF from 2020 provides a simple holistic pathway ("ABC") consisting of three main pillars to improve patients' outcome suffering of AF:

- A for Anticoagulation/ Avoid stroke
- B for Better symptom control
- C for Cardiovascular and Comorbidities optimization

1.8.1 Anticoagulation/ Avoid stroke

AF leads to an unrhythmic and uncoordinated contraction of the atria at high pace resulting in a decline in mechanical function as well as a nonlinear blood flow. Dilatation and stagnation of blood in the atria (especially in the appendages) leading to thrombus formation.(6) Therefore the risk of stroke and systemic thromboembolism is increased and measures like anticoagulation need to be taken.

1.8.1.1 CHA_2DS_2-VASc-Score

The CHA_2DS_2-VASc-Score is used worldwide to evaluate the risk of an AF-related stroke and therefor supporting the decision if the patient benefits from oral anticoagulation (OAC). This score offers a compromise between simplicity and precision making it ideal for a quick risk assessment in daily clinical use.(3) It represents the most common stroke risk factors:

RISK FACTORS		POINTS	DEFINITION
C	Congestive heart failure	1	Clinical HF, moderate-severe LV dysfunction or hypertrophic cardiomyopathy
H	Hypertension	1	Or on antihypertensive therapy; history of HT possibly caused vascular changes favouring stroke
A_2	Age: ≥75 years	2	Stroke risk rises from age 65 upwards
D	Diabetes mellitus	1	DM I and II increase risk for thromboembolic events similarly
S_2	Stroke	2	Previous stroke, transient ischemic attack or thromboembolism
V	Vascular disease	1	Peripheral arterial disease, coronary arterial disease, myocardial infarction are independent risk factors
A	Age: 65-74 years	1	
Sc	Sex category	1	Female = 1; Male = 0

Table 3: CHADS-VASC-Score for evaluation of stroke-risk in AF patients(3)

Its potential lies in identifying low-risk patients (scores: male=0; female=1) predicting a risk of stroke/ mortality in less than 1% per year. In high-risk patients it only performs moderate in forecasting thromboembolic events.(3)

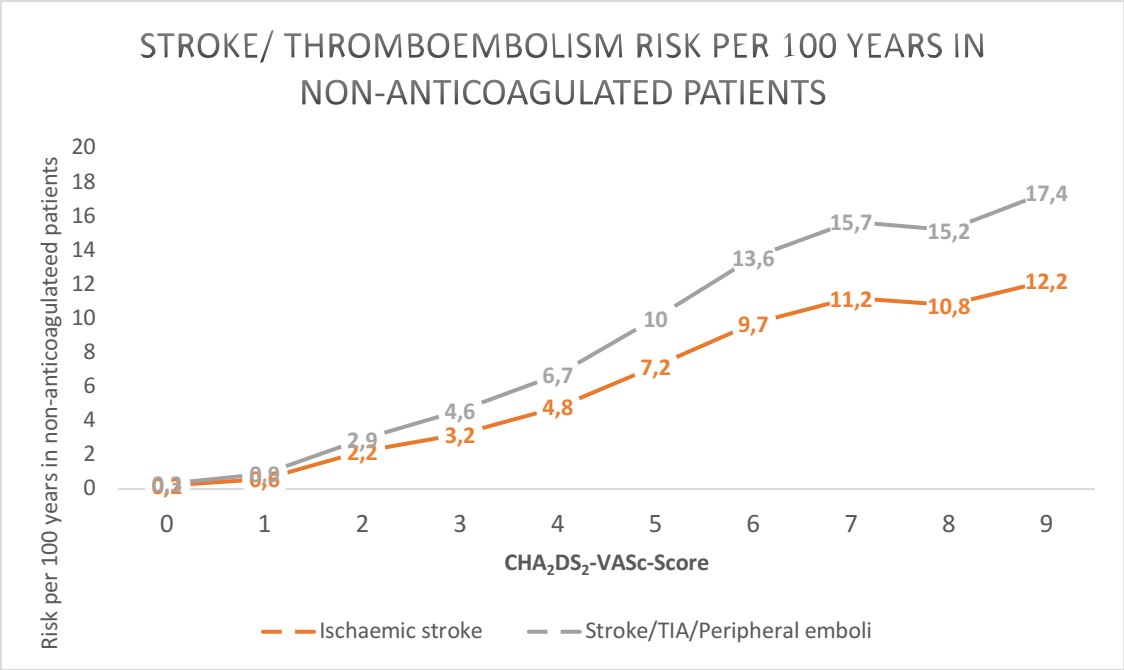

Figure 9: Stroke/ thromboembolic risk per 100 years in non-anticoagulated patients(18)

1.8.1.2 HAS-BLED-Score

Is a simple score to assess the 1-year risk for major bleeding (intracranial, hospitalization, haemoglobin decrease >2g/L, and/or transfusion) in patients using OAC with AF. If all patients with AF would receive anticoagulation without evaluating their individual risk profile around 1,5% of patients would suffer from an adverse event within 1 year of therapy.(26) Other scores like ATRIA and HEMORR2HAGES are available to assess the risk for adverse events of OAC as well but HAS-BLED is superior due to its ease in application and higher sensitivity.(27)

RISK FACTORS		POINTS	DEFINITION
H	(uncontrolled) Hypertension	1	Systolic BP > 160mmHg
A	Abnormal renal/ hepatic function	1 each	Dialysis, transplant, serum creatinine >200µmol/L, cirrhosis, etc.
S	Stroke	1	Ischaemic or haemorrhagic stroke
B	Bleeding history or predisposition	1	Major haemorrhage, anaemia or severe thrombocytopenia
L	Labile INR	1	Time in therapeutic range <60% in patients with Vitamin-K-Antagonists
E	Elderly	1	Age > 65 years
D	Drug or excessive alcohol drinking	1 each	Concomitant use of antiplatelet or NSAID; and/ or excessive alcohol use

Table 4: HAS-BLED score: risk for major bleeding for patients on OAC(22)

A maximum of 9 points can be reached indicating a very high risk for side effects of OAC. For patients with a high bleeding risk alternatives or a dose reduction should be taken into consideration. Scores ≤2 are usually no contraindication for use of anticoagulation.

HAS-BLED Score	Risk group	Risk of major bleeding (28)	Bleeds per 100 patient-years (26)	Recommendation
0	Relatively low	0,9%	1,13	Anticoagulation should be considered
1		3,4%	1,02	
2	Moderate	4,1%	1,88	Anticoagulation can be considered
3	High	5,8%	3,74	Alternatives to anticoagulation should be considered
4		8,9%	8,70	
5		9,1%	12,50	
>5*	Very high	-	-	

Table 5: Facts and Figures to HAS-BLED score(29)

*Scores greater than 5 were too rare to determine risk but are likely over 10%.(29)

1.8.2 Better Symptom control

As most patients start experiencing symptoms (e.g., chest pain, palpitations, weakness, dizziness) when AF or tachycardic episodes of AF occur it is crucial to lower burden to improve quality of life as well as to reduce mortality and morbidity. This can either be done by rate or rhythm control.

1.8.2.1 Rate control

The exact optimal goal for the heart rate is yet unknown. The RACE II trial (Rate Control Efficacy in Permanent Atrial Fibrillation) didn't show any benefit in neither quality of life nor symptoms in patients with strict targeted (<80 bpm) vs. lenient hear rate (<110 bpm).(30) For the initial targeted heart rate a lenient approach (<110 bpm) seems to be best for most patients, unless the burden of symptoms requires a stricter control.(3)

Beta-blockers, digoxin, diltiazem, and verapamil can be used to a achieve a heart rate reduction as first-line treatment. The choice of medication is depending on comorbidities (HF, COPD, Asthma, etc.).

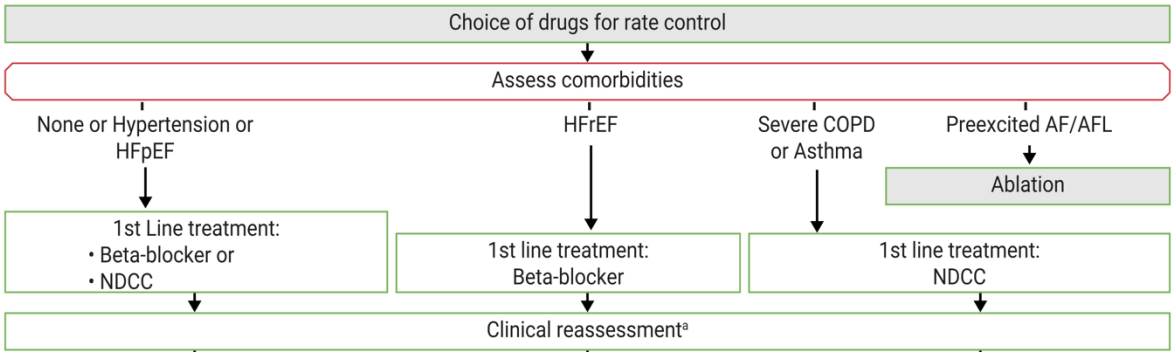

Figure 10: Choice of rate control drugs(3)

If the initial goal (heart rate <110 bpm, improving symptoms or better quality of life) cannot be met a step-up therapy with a 2nd drug can be started. As 3rd line therapy a combination of 3 drugs, implantation of pacemaker with AV-node ablation or evaluation for a cardiac resynchronisation therapy device can be used.(3)

The AFFIRM trial (Atrial Fibrillation Follow-up Investigation of Rhythm Management) showed that pharmacological rate control (<80 bpm) can be achieved in 58% of all patients. The most effective drugs were beta blockers (achieved an effective heart rate reduction in 70% followed by digoxin 58% and calcium channel blockers 54%) alone or in combination with another drug.(31)

1.8.2.2 Rhythm control

The aim is to re-establish a sinus rhythm and preserve it as long as possible to reduce burden of symptoms and improve quality of life. This can be achieved by catheter ablation, electrical or pharmacological cardioversion.

The EAST-AFNET4 Trial (Early treatment of Atrial Fibrillation for Stroke prevention) was able to detect significant benefits for early rhythm control therapy (pharmacological or catheter ablation) vs. usual care (rate control, no specific therapy or symptom therapy) in comparison of severe adverse events (death, stroke, acute coronary syndrome (ACS), worsening HF, hospitalization) (HR, 0.79; 96% CI 0.66–0.94; P = 0.005)..(32)

If rhythm control therapy is considered it should be started early as AF progression otherwise becomes less responsive to treatment.(3)

Electrical cardioversion:

Synchronized, biphasic direct current cardioversion is the go-to method for a hemodynamical unstable patient as its onset is much faster compared to pharmacological cardioversion. In non-emergency situation electrical cardioversion can be performed immediately within 48h after onset – otherwise formation of a thrombus in the atria must be excluded first if the patient is not taking OAC credibly.(3)

Yet it is unclear whether immediate electrical cardioversion within 48h is beneficial as AF can spontaneously convert back to sinus rhythm in the early beginning but also because sedation and electrical burns can cause harm to the patient. A smaller study showed non inferiority for a delayed electrical cardioversion (after 48h of onset, initial treatment with rate-control medication) as opposed to early cardioversion in cardiorespiratory stable patients.(33)

Pharmacological cardioversion:

Should only be used in hemodynamically stable patients. The efficiency might be biased as onset time of the anti-arrhythmic drugs and spontaneous conversion into sinus rhythm may overlap and a true differentiation of the cause for conversion is not possible. Therefore, a "wait-and-watch" strategy (<24h) might be considered.(33) On the other hand, pharmacological cardioversion has a higher success rate directly after onset. The choice of the anti-arrhythmic drug should be based on severity of burden and past medical history (left

ventricular hypertrophy, left ventricular systolic dysfunction, ischaemic heart disease etc.).(3)

Catheter ablation:

Catheter ablation (CA) can help maintaining sinus rhythm effectively, reduce symptoms and improve quality of life more likely than anti arrhythmic drug therapy.(34-36) A Meta-analysis performed by Mao et al. showed a significant reduction in all-cause mortality for HF patients with AF who received a CA – especially if the follow-up time was >12 months.(35) Particularly patients with HF and AF-mediated tachycardia-induced cardiomyopathy benefit from CA.(3) A recent multicentre prospective controlled study (CASTLE-AF) compared the outcome of patients suffering from AF and HF (LVEF <35%) either receiving CA or rhythm-control therapy. They found that CA was able to reduce the burden of AF significantly compared to pharmacological therapy. Furthermore, when the burden of AF could be reduced to <50% there was a significant reduction in primary endpoint (death or hospitalisation due to worsening of HF) and all-cause mortality.(37) In general, CA is recommended as first-line if preferred from patient but also as second-line treatment after failure/ intolerance of anti-arrhythmic drugs. Performed by trained operators it is a safe and well-established treatment. Complications can occur in about 4-14% of ablations, of which up to 3% are potentially life-threatening. In centres with high experience, the complication rate is on the lower side. Deaths during the procedure are rare (<0.2%) and mostly due to pericardial tamponade.(3)

As ablation also poses a risk for suffering of periprocedural stroke, major bleeding, pulmonary vein stenosis and pericardial complications, negative predicting factors for recurrence of AF (e.g., enlarged left atria, prolonged duration of AF, increased patient age, renal dysfunction, substrate visualization on magnetic resonance imaging (MRI)) should be taken into consideration when deciding to adopt for an invasive rhythm control strategy.(3, 35)

1.8.3 Cardiovascular risk factors and concomitant diseases

Identification of cardiovascular risk factors and comorbidities, including lifestyle factors and other pre-existing medical conditions, significantly influence lifetime risk for developing AF. Therefore, in addition to treating AF itself, it is extremely important to treat other underlying conditions safely and effectively to prevent/ delay the possible progression of AF.

Risk factors/ Comorbidities:

Hypertension, heart failure, coronary artery disease, diabetes mellitus and sleep apnoea are known risk factors for AF (for further details see chapter 1.6).

The RACE 3 trial (Routine versus Aggressive upstream rhythm Control therapy for prevention of Early atrial fibrillation in heart failure) showed a significant (75% vs 63%) presence of sinus rhythm 1 year after rhythm control therapy initiation in patients with an extended medical therapy vs conventional treatment. The additional therapy consisted of mineralocorticoid receptor antagonists, statins, angiotensin converting enzyme inhibitors, receptor blockers and cardiac rehabilitation including physical activity, dietary restrictions, and counselling.(38)

Lifestyle interventions:

Elevated body mass index (BMI) increases risk for AF and may additionally increase the likelihood of stroke and subsequent death.(39) Weight reduction also reduces blood pressure, blood lipids and the risk of developing type 2 diabetes mellitus and can therefore significantly reduce cardiovascular risk.(40)

Excessive alcohol consumption on the one hand increases the occurrence of AF and on the other hand also affects the risk of bleeding under OAC due to falls.(26) In high concentrations alcohol also increases the risk of thrombosis and death.(41)

Regular coffee consumption does not seem to increase the occurrence of AF, habitual caffeine consumption might even lower the risk.(42) Palpitations of any origin may be perceived more strongly.

Moderate physical activity has a positive effect on cardiovascular health.(43) The occurrence of AF seems to be more frequent in professional athletes (especially in the endurance field: marathon, long-distance-triathlon).(44) Patients should be encouraged to engage in moderate physical activity, but excessive endurance sessions should be avoided.

2 Arterial hypertension

Arterial hypertension is defined as a systolic blood pressure ≥140mmHg and/ or diastolic blood pressure ≥90mmHg.(40, 45) The graduation of hypertension can be divided into different degrees of severity:

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120-129	and/or	80-84
High normal	130-139	and/or	85-89
Grade 1 hypertension	140-159	and/or	90-99
Grade 2 hypertension	160-179	and/or	100-109
Grade 3 hypertension	≥180	and/or	≥110

Table 6: Classification of blood pressure and definition of hypertensive grade(45)

These cut off value are somewhat arbitrary as the relationship between blood pressure and cardiovascular diseases (CVD) and renal events is gradual – 140mmHg are a good threshold value at which the benefits from therapy outweigh the possible drug side effects.(45)

2.1 Epidemiology

Arterial hypertension is the most common internal medicine disease worldwide, affecting about 1 billion people in 2019. Globally of all adults aged 30-79 years 32% of women and 34% of men are impaired.(46) Only about 47% of patients are aware of their diagnosis, with BP control among 33% of those being treated. Hypertension progressively increases with advancing age, more than 60% of people aged >60 years are affected.(47) Due to increasing age of population around 1,5 billion people are estimated to be impacted in 2025.(48) Furthermore, it is the leading cause of premature death although it is preventable if measures are taken at an early stage.(46)

2.2 Aetiology

Hypertension can be divided into two groups depending on the origin:(8)

- **Primary hypertension** (>90%)

  Primary or essential hypertension is defined as high blood pressure for which no secondary causes could be found (diagnosis of exclusion). It usually develops after the age of 30 and is of multifactorial origin (increased age, obesity, dyslipidaemia, unhealthy lifestyle, familial risk factors, low socioeconomic status, inadequate nutrition).

- **Secondary hypertension** (ca. 10%)

  Is caused by various comorbidities, the most common of which are as follows:

  - Obstructive sleep apnoea syndrome
  - Renal hypertension (renal artery stenosis, renal parenchymal disease, chronic kidney disease)
  - Endocrine hypertension (hyperthyroidism, primary hyperaldosteronism, pheochromocytoma, hypercortisolism, etc.)
  - Other (aortic coarctation, aortic stenosis, toxic, drugs, etc.)

2.3 Cardiovascular risk assessment

Hypertension often occurs with other risk factors thus, making it an important part in quantification of total cardiovascular risk. The 2021 ESC Guidelines on cardiovascular disease prevention recommend using the updated SCORE2 algorithm (Systematic COronary Risk Evaluation) to evaluate an individual's 10-year risk of fatal and non-fatal CVD event. The cardiovascular mortality rates are influenced by the geographical location. Therefore, the ESC guideline provides different tables for different risk regions (low, moderate, high, very high). Depending on gender, age and smoking behaviour, the patient's CVD risk can be assessed, based on the systolic blood pressure value and the non-HDL cholesterol value.(49)

Patients with atherosclerotic cardiovascular disease, diabetes mellitus (type 1 or type 2), chronic kidney disease or familiar hypercholesterolaemia are at a higher risk to develop a CVD. Further intensification of risk factor treatment should be considered in these patients.(49)

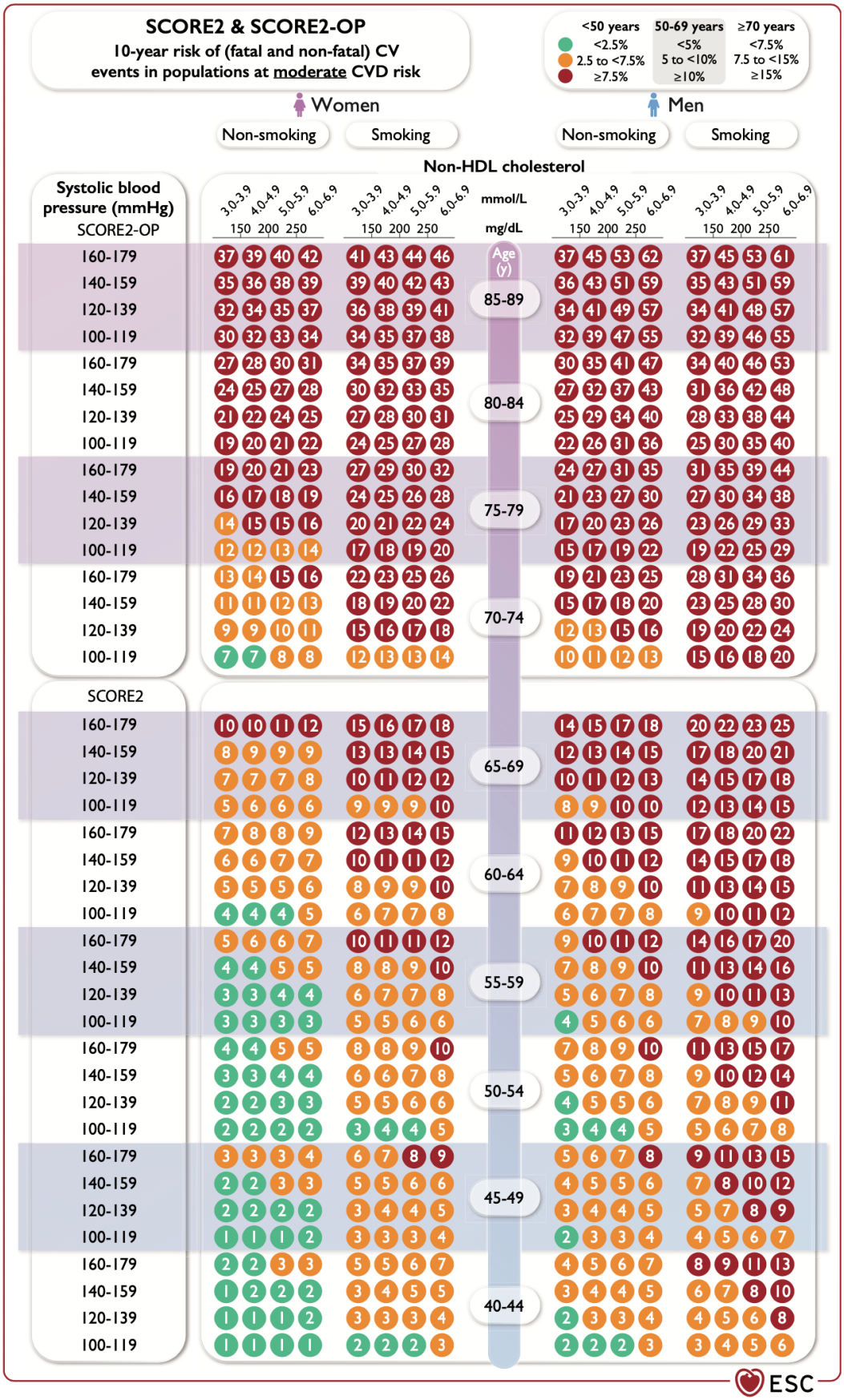

Figure 11: SCORE2-Algorithm to estimate the risk of fatal and non-fatal CVD in a moderate-risk country(49)

2.4 Benefits of reduced BP

Lowering the blood pressure by 10mmHg the all-cause mortality significantly decreases by 13% - irrespective of the patients baseline.(50) The relative risk for major cardiovascular events (0,80), coronary heart disease (0,83), stroke (0,73) and heart failure (0,72) declined in the studied population (123 randomized controlled trials (RCTs) including approximately 614.000 patients) significantly as well.(50) Thomopoulos et al. provided similar significant numbers in another meta-analysis including 63 RCTs involving a total number of 246.000 patients.(51)

2.5 Treatment

The ESC guideline for the management of arterial hypertension 2018 recommends achieving a first BP goal of <140/90mmHg in all patients – if the treatment is tolerated well the BP can then be lowered to <130/85mmHg.(45, 50)
For elderly patients (>65 years, irrespective of cardiovascular risk or CVD) an ideal systolic BP range is 130-139mmHg with close monitoring of side-effects due to treatment.(45)

A major problem in the treatment of hypertension is compliance. Patients often do not experience any symptoms and therefore do not suffer, which is why adherence is low. This problem can best be solved through improved doctor-patient communication.(52)

2.5.1 Non-pharmacological interventions

Lifestyle optimisation can delay or even prevent the onset of hypertension, especially in grade 1 hypertension. In patients with hypertension mediated organ dysfunction or high risk for cardiovascular events lifestyle intervention can be supportive but should not delay pharmacological therapy.
Salt restriction, reduction of alcohol consumption, smoking cessation, increased vegetables and fruits intake, weight reduction and maintaining an ideal weight and physical activity have shown to reduce BP effectively.(45)

2.5.2 Pharmacological interventions

For most patients' lifestyle interventions are not enough to obtain normal blood pressure. Therefore, the ESC Guideline for management of arterial hypertension 2018 recommends the use of 5 different classes for treatment (alphabetical order):

- Angiotensin-converting enzyme inhibitors (ACE)
- Angiotensin receptor blockers (ARB)
- Beta blockers
- Calcium channel blockers (CCB)
- Diuretics (thiazides, thiazide-like)

In large meta-analysis these classes of drugs have proven to lower the BP effectively and reduce the cardiovascular risk.(50, 51)

Studies have confirmed that it is more effective (better BP control, fewer side effects) to start BP therapy with a combination preparation of two drug classes than to exhaust a monotherapy.(53, 54) Chow et al. provided evidence that it is even possible to start a fixed-dose quadruple combination therapy and achieve better efficacy, tolerability and similar side-effects compared to monotherapy.(55) To improve the compliance and persistence of the patient it is recommended to use a 1 pill strategy because more pills only lead to less adherence to therapy.(56)

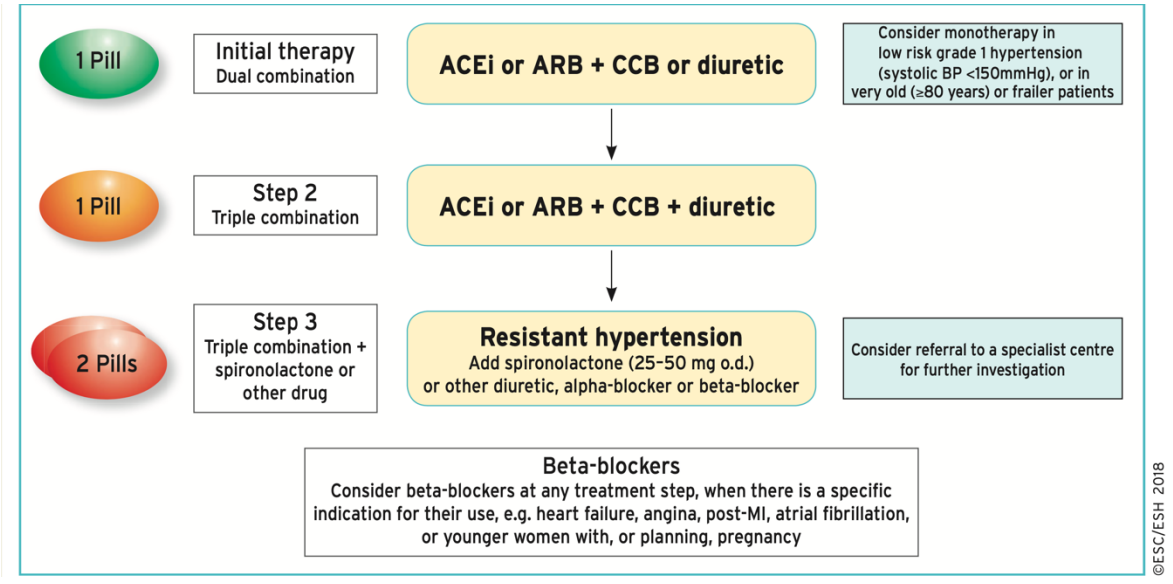

Figure 12: ESC2018 treatment algorithm for uncomplicated hypertension(45)

3 Materials and methods

An extensive literature search was conducted to prepare this thesis. To be able to provide an overview of the current state of knowledge on the topics of AF and AHT, medical databases such as PubMed, UptoDate, ClinicalTrials.gov and ScienceDirect were searched for recent scientific articles.

The aim of this thesis is to provide an overview of the influence of AHT on the development and perpetuation of AF as well as up-to-date available therapeutic options for both diseases. Ultimately appropriate evidence-based therapy in the presence of AF combined with AHT as the most common isolated risk factor will be highlighted.

4 Results

The 2018 ESC guidelines for the management of AHT mention in their latest update accumulating evidence for linking hypertension with an increased risk of developing AF.(21) AF and AHT often occur together because AHT increases the incidence of AF and these two entities have common risk factors that increase the incidence of both conditions.
Hypertension is the most prevalent disease contributing to AF. The Framingham study was able to show that AHT was responsible for more new-onset AF cases than any other risk-factor.(57)
Even high normal blood pressure can promote the development of AF, yet the exact BP threshold is not known. Grundvold et al. showed that men with a systolic BP of ≥140mmHg or upper normal BP had a 1,60-fold and 1,50-fold increased risk of incident AF compared to men with a BP <128mmHg. An elevated diastolic BP of ≥80mmHg increased the risk 1,80-fold in contrast to diastolic BPs <80mmHg.(58)

As opposed to most other risk-factors AHT is potentially modifiable by lifestyle changes (stress reduction, active exercise, healthy diet, weight reduction), highlighting its importance in prevention of the arrhythmia. In 50-90% of all patients suffering from AF hypertensive blood pressures can be measured.(59)

4.1 The influence of arterial hypertension on AF

Maintenance of AF requires alteration of the atrial substrate (particularly the left atrium) by electrical and structural changes. The exact mechanisms and how arterial hypertension influences these changes will be discussed in the following chapters.

4.1.1 Structural remodeling

Cardiac remodeling occurs as cardiomyocytes try to maintain homeostasis against external stressors to preserve cardiac function. This remodeling process of the atria are time-dependent and dependent of the intensity of the volume and/or pressure load.(60) Atrial structural remodeling is a major factor for promoting re-entrant mechanisms. It usually appears after a few weeks or months of AF and implies microscopic and macroscopic changes in the atrial myocardium. Progressive atrial dilatation is the most predominant aspect of atrial remodeling, which can support re-entry mechanisms directly by producing larger pathways. Furthermore, it strongly correlates to presence of fibrosis leading to a heterogeneity of slow-conducting pathways for electrical conduction favouring development and maintenance of AF.(22, 61) This process is mainly driven by an up-regulation of collagen I, III and ST2.(62) Histological animal and post mortem human studies found an association between AF and progressive atrial fibrosis. (63) AF itself induces changes in the atrial myocardium leading to increased sustainability of AF – as authors conclude "AF begets AF".(22)

A recent animal study found that structural remodeling may be Ca^{2+}-dependent in mice. Genetic ablation of ryanodine receptor typ-2 hyperphosphorylation reduces sarcoplasmic Ca^{2+}-leak, thereby may help preventing atrial dilatation, atrial conduction abnormalities and progression of AF.(64)

Atrial fibrosis can be detected non-invasively by means of late gadolinium enhancement MRI. Clinical studies investigate on evaluating and quantification of atrial fibrosis before a planned catheter ablation for persistent AF and whether targeting specific atrial fibrotic tissue may increase the success rate. As the preliminary results from the DECAAF II (Delayed-Enhancement MRI Determination of Successful Radiofrequency Catheter Ablation of Atrial Fibrillation) trial showed atrial fibrosis is an independent risk factor for AF recurrence after catheter ablation but the study failed to show an improvement of

outcomes in targeting fibrotic tissue especially when the atrium was already affected by fibrotic remodeling of >20% of atrial tissue.(65, 66)

4.1.1.1 Influence of arterial hypertension

AHT leads to reduced left ventricular compliance, diastolic dysfunction, left ventricular hypertrophy and left atrial enlargement which can eventually support the development of AF.(45) Left ventricular hypertrophy is the most relevant structural correlate because it causes increased stiffness of the LV, increased wall tension and filling pressure as well as higher activation of the sympathetic nervous system and the renin-angiotensin-aldosterone-system.(59) These processes lead to an increased pressure and stretch in the left atrium (LA) which then favour remodeling of the myocardium.(67)

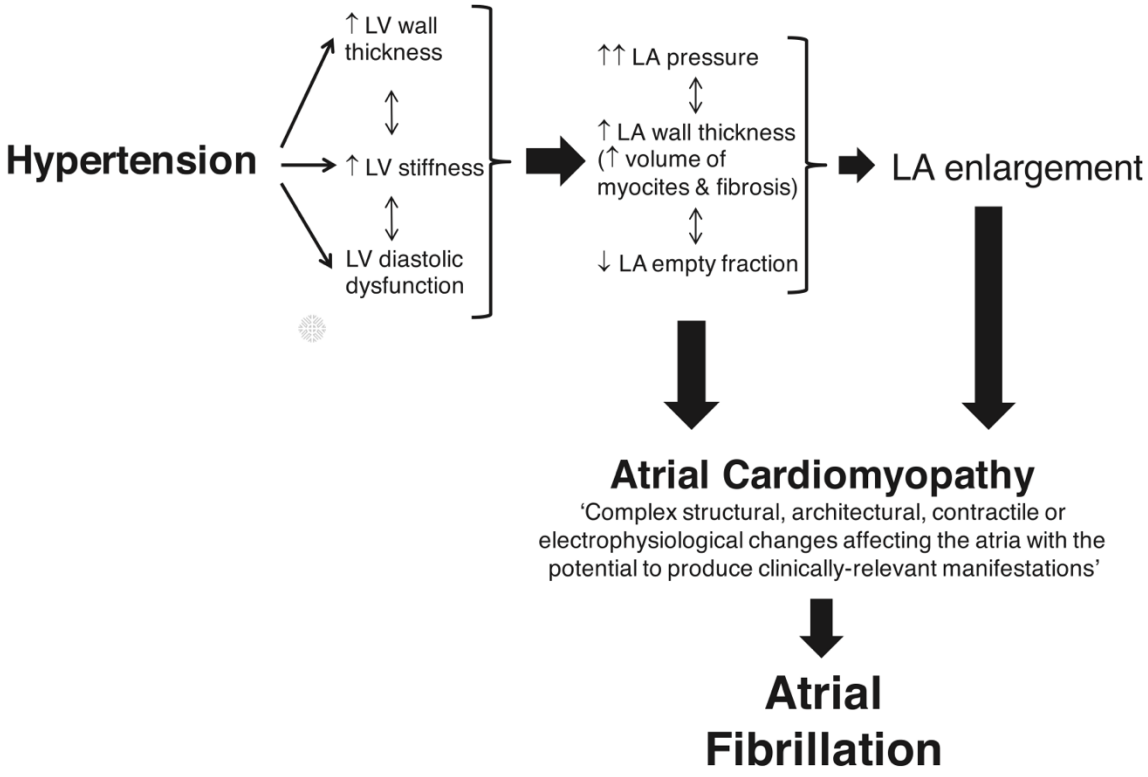

Figure 13: Potential mechanisms by which hypertension may favour the onset of AF(67)

The group of Manninger M. et al analysed the influence of arterial hypertension in AF on structural and electrical changes of the atria in a porcine model: one cohort of pigs were implanted with an AAI-pacemaker and developed AF by rapid atrial pacing (RAP), while the other group underwent deoxycorticosterone acetate (DOCA) pellet implantation as an add-on to induce arterial hypertension. The size and weight of the atria was significantly bigger in the DOCA group compared to pigs with AF without concomitant AHT.

Stereological analysis revealed an increase in collagen volume (especially non-intermyocyte collagen = collagen between muscle bundles and perivascular regions). There was no difference in mitochondrial, sarcoplasmic, nucleic or myocyte and myofibril volume. So AHT as risk factor for AF induces early and more pronounced cardiomyocyte hypertrophy as well as fibrotic remodeling.(5)

4.1.2 Electrical remodeling

In 1995 Wijffels et al. described the first concept of electrical remodeling in a goat study with induced AF. They laid the foundation for further research in this field.(68)
During AF electrical restructuring is happening in the atria, affecting the effective refractory period of the atrial myocardium which is essential for AF to occur. The electrical disturbance of the atrial myocardium further aggravates the damage to the atrial tissue structure, this reduces the self-compensatory reserve function and ultimately leads to fibrotic and dysfunctional remodeling. The resulting structural remodeling in turn leads to electrical dysfunction of the myocardium, which promotes the development of persistent or permanent AF. The electrical changes in the atria are due to the increased atrial frequency caused by AF itself. This process indicates long-term changes in electrophysiological parameters resulting in altered ion channel function.(60)

The electrical remodeling in patients with AF consists mainly of three changes: increased Ca^{2+} concentration, decreased L-type calcium current (I_{CaL}) and reduction in atrial effective refractory periods (AERP).(62)
A reduction in I_{CaL} and/ or increased repolarizing currents (I_{K1} and $I_{K,Ach}$) can result in a shorter atrial action potential duration (APD), shorter AERP, and changes in refractory period adaptation to rate and therefore promote reentry mechanisms.(60, 61)
A Study of Parra and Rothermel showed that Calcineurin/ nuclear factor of activated T-cell (NFAT) pathways are involved in electrical remodeling. By decreasing I_{CaL} density and shortening of the APD it increases the likelihood of initiation and perpetuation of AF.(62)

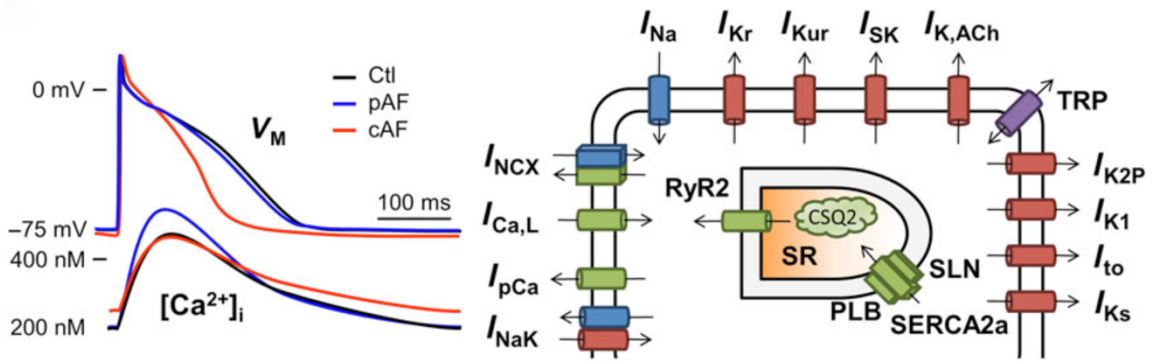

Figure 14: Atrial electrophysiology and basic arrhythmogenic mechanisms(61)

This figure shows a normal action potential (AP) and Ca^{2+}-transients in a sinus rhythm (Ctl), as well as in paroxysmal AF (pAF) and long-standing persistent (chronic) AF (cAF). The shortened AP in patients with cAF is mainly due to a reduced I_{CaL} and increase in repolarisation currents. As the APD in patients with pAF is not impaired the suspicion is that the reduced APD is due to AF itself.(61) The reduction in I_{CaL} is likely to be an adaptive mechanism of the cell to protect itself from toxic Ca^{2+}-accumulation due to high atrial rates. This effect only becomes significant if the atrial rates exist long enough.(69)
The right part shows a schematic overview of atrial ion channels and Ca^{2+}-handling proteins.(61)

Increased inward rectifier K^+-currents produce resting membrane potential hyperpolarization which then lead to enhanced excitability.(61)

Electrical remodeling can further change the expression, function, or localization of connexins. Connexins are gap-junctions which allow a fast and direct communication between cells via transportation of ions and second messenger. This cell-to-cell electrical coupling can be altered, leading to re-entry-promoting slow and/ or heterogeneous conduction.(61)

Some investigators consider electrical remodeling as a compensatory mechanism of the atrium and develops only because of AF, as no cumulative damage to atrial structures was noted after AF ceased. The authors consider it a physiological protective function to prevent further AF.(60) It was shown in an animal model that this process (reduction of APD as well as shortening of the AERP) were reversible after restoring sinus rhythm and keeping the animals in a normal heart rhythm for several days to weeks.(68)

4.1.2.1 Influence of arterial hypertension

In a porcine experimental model, AF was induced in 18 pigs by continuous fast right-atrial pacing (600 bpm) using custom-made pacemakers. In 9 of these pigs, secondary hypertension was additionally induced by using deoxycorticosterone acetate (DOCA). The group of investigators didn't find any differences in left and right AERP or APD.(5)

Left and right AERP as well as APD90 were comparable between both groups at every pacing cycle length (CL) as well as left and right atrial endocardial conduction velocity. On a multielectrode array with a pacing CL of 250-500ms there was no difference in epicardial conduction velocity. Even during mapping while AF was present there was no difference in complexity, AF CL, waves per CL or mean conduction velocity between both groups. The authors concluded that the stability of AF in this test setup was not influenced by electrophysiological changes. The main pathway in which AHT influenced AF stability was by atrial dilatation.(5)

4.2 Therapeutic strategies to target AHT and AF

The best way of treatment is still to prevent the occurrence of the disease by reducing risk-factors and optimizing lifestyle habits. The changes in the myocardium of the heart induced by pathophysiological processes are partially irreversible, which then makes a therapeutic success more difficult.

Regarding the risk factor AHT, there are two scenarios: Hypertension present but no AF yet with the goal of preventing the arrhythmia from occurring and AHT and AF both present with the goal of obtaining the best possible therapy for both diseases.

4.2.1 Prevention of AF in hypertensive patients

ACEis and ARBs have shown to reduce first occurrence of AF in hypertensive patients with left ventricular hypertrophy and/ or high cardiovascular risk compared with CCBs or beta-blockers.(70, 71) This effect may be due to more effective LV structural regression and improved LV function.(72) Angiotensin II may lead to pro-arrhythmogenic changes in atrial cells by altering ion channels. It also promotes hypertrophy and fibrosis of atrial myocytes, which may result in overall structural and electrical remodeling.(71) ACEis and ARBs do not avoid reoccurrence of paroxysmal or persistent AF.

In a large Danish study, 5 typical antihypertensive-monotherapy drug groups (ACEi, ARB, CCB, diuretics, betablocker) were compared with respect to the incidence of new-onset AF. It should be emphasized that patients at risk for developing AF (e.g., Patients with HF, ischaemic heart disease, diabetes mellitus, or hyperthyroidism) were excluded. ACEis and ARBs in monotherapy have been shown to reduce the incidence of AF compared with beta-blockers. The authors note that this is a retrospective study in which beta-blockers may have been prescribed to patients suspected of developing AF (e.g., patients who report of palpitations) to induce rate-control beforehand and therefore falsify the results of betablockers.(73) This study supports the results of an earlier published study from England in 2010, which had observed likewise results.(74)

In 2016 a study in Taiwan included 25.000 patients with hypertension and divided them into 3 groups, depending on their anti-hypertensive medication: ACEi-users, ARB-users and none-users. Their goal was to find new onset-AF. The authors conclude that ACEi and ARB are both capable of preventing new-onset AF in patients with and without risk-factors for occurrence of the arrhythmia. ARBs tend to be more effective in patients who previously had a stroke or TIA.(75)

4.2.2 Therapy of co-existing AHT and AF

As patients with AF tend to have a higher ventricular rate an anti-hypertensive therapy with beta-blockers or non-dihydropyridine calcium antagonists should be considered if rate control is desired. If the patient suffers from reduced LV-function non-dihydropyridine calcium antagonists should be avoided, as they can trigger HF.(45)

Xu et al. enrolled 1110 patients in an emergency department with AHT and AF. They compared patients receiving ACEis/ ARBs with patients who did not and followed them up for 1 year to evaluate patients' outcome. The use of other prescribed medication (e.g., betablocker, dihydropyridine CCB, digoxin, aspirin, statins, or amiodarone) did not influence the allocation at all. The authors conclude that ACEis/ ARBs reduced the risk of all-cause death (HR, 0.605; 95% CI 0.431–0.849; P = 0.004), risk of cardiovascular death (HR 0.585; 95% CI 0.372–0.921; P = 0.020) and major adverse events (HR 0.651, 95% CI 0.496–0.855, P = 0.002) after adjusting for other risk factors.(76)

5 Conclusion

Although tremendous research progress has been made in recent years regarding the mechanisms of origin and pathophysiology of AF, there are still several gaps in evidence. Structural remodeling processes appear to be the sign of prolonged phases of AF, are responsible for resistance to therapy, and contribute to persistence of this arrhythmia. Within the last years focus of research has been on trying to understand mechanisms and finding new therapeutic targets to improve outcomes of patients especially to improve success rates of catheter ablation. For now, no general pathway to target non pulmonary vein triggers has shown improved efficacy. In the coming years, processes such as fat accumulation, oedema, amyloidosis, interaction between myofibroblasts and cardiomyocytes, and other yet unknown factors may be new approaches to gain more insight of pathophysiological processes in AF. Currently it is not clear to what extent these individual factors contribute to the development and maintenance of AF.

Animal models are a widely used method in the study of pathophysiological processes in AF. However, they have some important limitations: only few models describe a spontaneous occurrence of AF, like it is seen in clinical patients. Most of the time electrical stimuli are required for AF onset in order to observe changes in the myocardium. Animal models usually focus on an isolated pathophysiological trigger (e.g., hypertension, heart failure, ischemia, etc) that is applied to induce AF as quickly as possible. Clinically, AF usually develops due to multiple disease, long-standing pathophysiologic processes, and multiple pharmacotherapeutic influences. All these influencing factors mentioned before are present over months to years in real patients. The time-gap between trigger and AF induction in animal studies are usually just about weeks. These are reasons why animal models are sometimes not applicable in real patients. However, they do provide important seminal insights into possible mechanisms of development, which, like a puzzle, eventually present us with the whole picture. Animal models are necessary to establish correlations between causes of AF and their cellular mechanisms to offer evidence for specific therapeutic strategies. The causes of AF are diverse. It should be viewed less as a disease than as the product of a variety of clinical conditions, some of which may prevail for years and eventually present as AF.

Concerning the therapeutic strategy of patients with arterial hypertension as the most important risk factor of AF, the current literature is consistent with the recommendation of the 2018 ESC/ESH Clinical Practice Guidelines for the Management of Arterial Hypertension.
Initial antihypertensive therapy should be started with a dual combination therapy consisting of ACEi or ARB combined with beta blocker or non-dihydropyridine CCB - preferably as one pill. If blood pressure reduction is insufficient, it should then be increased to a triple therapy. This therapy approach is ideal for both cases: if the patient does not suffer from AF, ACEis/ ARBs may prevent occurrence of AF. If, on the other side, the patient is affected by AF, betablocker/ CCB can reduce the ventricular rate and therefor reduce the burden of the arrhythmia.(45)

6 Discussion

Atrial fibrillation is the most common arrhythmia in humans and already affects more than 59 million in 2019. In the coming years, a significant increase will be observed due to higher life expectancy. A major risk factor for its development is arterial hypertension, which can often be influenced by lifestyle changes. It is also a common clinical picture in internal medicine. Due to similar risk factors, these two diseases often occur together. Current research shows that even a slight increase in systolic or diastolic blood pressure significantly increases the risk of developing atrial fibrillation.

Despite intensive research in recent years into the development and maintenance of atrial fibrillation, the exact mechanisms are not yet known. Both triggering factors and reentry mechanisms can be responsible for the development and perpetuation of atrial fibrillation. Underlying changes involve structural remodelling as well as electrical changes in the atrium (mainly left atrium). Structural remodelling includes dilatation of the atria and increasing fibrosis, both processes are favoured by arterial hypertension. The dilatation of the left atrium in particular can be used as a predictive value for the development of atrial fibrillation. It should also be mentioned that atrial fibrillation itself contributes to its own maintenance through the above-mentioned mechanisms – “AF begets AF”.
Electrical remodelling focuses on a shortening of the action potential duration due to changes in ion channels (mainly Ca^{2+}-channels). However, scientists suspect that these changes occur

mainly in the context of atrial fibrillation and are protective mechanisms of the heart against further damage. The electrical changes were reversible after sinus rhythm was restored. This could be shown in an animal experiment with goats. In another animal experiment with pigs and induced arterial hypertension, it could be shown that (at least with short-term induction of atrial fibrillation) there were no significant differences between the groups with and without hypertension.

Apart from lifestyle changes, the drug therapy for arterial hypertension is based on preventing the occurrence of atrial fibrillation with classical RAAS-inhibitors as ACEis and ARBs. In the case of already existing atrial fibrillation, on reducing the symptoms by lowering the heart rate (betablockers and CCBs). This can ideally be achieved by dual therapy (initial hypertension treatment with two drug groups in one pill) as recommended by the ESC 2018.

Further research will be needed in the future to investigate the exact mechanisms of development and maintenance. These results are necessary in order to be able to intervene at an early stage to prevent structural and electrical changes in the heart caused by arterial hypertension and atrial fibrillation.

7 Bibliography

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