Dissertation

Prevention of atrial fibrillation and its sequelae after cardiac interventions

submitted by

Dr. med.univ. David Zweiker

For the Academic Degree of

Doctor of Medical Science

(Dr. scient. med.)

at the

Medical University of Graz

Division of Cardiology

Department of Internal Medicine

under the supervision of

Assoc.Prof. Priv.Doz. Dr.med. Daniel Scherr

co-supervisors

Assoc.Prof. Priv.Doz. Dr.med.univ. Dr.scient.med. Peter Rainer

Priv.Doz. DI Dr. Günter Schreier, MSc

Graz, 11 December 2020

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 organizations that have contributed to the research of this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the guidelines of "Good Scientific Practice".

Graz, December 2020 *David Zweiker*

Disclosures

Parts of this thesis have been published in the following manuscripts:

Zweiker, D;[1] Sieghartsleitner, R; [1] Fiedler, L;[2] Toth-Gayor G; [1] Luha, O;[1] Stix, G;[3] Gabriel, H;[3] Vock, P;[4] Lileg, B;[4] Strouhal, A;[5] Delle-Karth, G;[5] Pfeffer, M;[2] Aichinger, J;[6] Tkalec, W;[6] Steinwender, C;[7] Sihorsch, K;[7] Binder, RK;[8] Rammer, M;[8] Barbieri, F;[9] Mueller, S;[9] Verheyen, N; [1] Ablasser, K; [1] Zirlik, A; [1] Scherr, D.[1] Indications and Outcome in Patients Undergoing Left Atrial Appendage Closure—The Austrian LAAC Registry. *J. Clin. Med.* 2020, *9*, 3274. DOI: 10.3390/jcm9103274

[1] Department of Cardiology, Medical University of Graz, Graz , Austria

[2] Department of Internal Medicine, Cardiology and Nephrology, Hospital Wiener Neustadt, Wiener Neustadt, Austria

[3] Department of Internal Medicine II, Medical University of Vienna, 1090 Vienna , Austria

[4] Department of Internal Medicine III, University Hospital St. Pölten, Austria

[5] Department of Cardiology, Hospital Nord-Klinik Floridsdorf, 1210 Vienna , Austria;

[6] Department of Internal Medicine II, Elisabethinen Hospital, 4020 Linz, Austria;

[7] Department of Cardiology, Kepler University Hospital, 4020 Linz, Austria;

[8] Department of Internal Medicine II, Klinikum Wels-Grieskirchen, 4600 Wels, Austria;

[9] Department of Internal Medicine III, Medical University of Innsbruck, 6020 Innsbruck, Austria

therefore *may be reused without permission provided that the original article is clearly cited*. More information is available at https://www.mdpi.com/openaccess.

Zweiker, D;[1] Fröschl, M; [1] Tiede, S; [1] Weidinger, P; [1] Schmid, J; [1] Manninger, M; [1] Brussee, H; [1] Zweiker, R; [1] Binder, J; [1] Mächler, H; [2] Marte, W; [3] Maier, R; [1] Luha, O; [1] Schmidt, A; [1] Scherr, D. [1] Atrial fibrillation in transcatheter aortic valve implantation patients: Incidence, outcome and predictors of new onset. J Electrocardiol. 2017; 50(4):402-409. DOI: 10.1016/j.jelectrocard.2017.02.013

[1] Department of Cardiology, Medical University of Graz, Graz, Austria

[2] Department of Cardiac Surgery, Medical University of Graz, Graz, Austria

[3] Department of Anaesthesiology, Medical University of Graz, Graz, Austria

All co-authors and their institutions explicitly agreed to the use of their data in this thesis. Additional manuscripts and abstracts that were created during the doctoral study are listed in the Appendix.

Doctoral student David Zweiker received funding from the Medical University of Graz through the Doctoral School Translational Molecular and Cellular Biosciences and the Department of Cardiology.

Preface

This dissertation gives an overview of my main research interest during my doctoral study at the Medical University of Graz. My main fields of interest lie in cardiac arrhythmias, especially atrial fibrillation (AF). I was fortunate to participate in a variety of studies at the Medical University of Graz, exploring AF in all its facets "from bench to bedside" – from animal models to registries, phase III studies and to academic prospective clinical trials.

During my first months working as a clinician, I became particularly interested in cardiovascular implantable electronic devices (CIEDs). My advisor Daniel Scherr already collaborated with the Austrian Institute of Technology (AIT) focusing on AF prediction algorithms, which estimate the occurrence of AF from a standard electrocardiogram (ECG) tracing. To utilize the outstanding monitoring advantages of today's CIED technologies, we initiated the prospective SAFE-ME study to evaluate the effectiveness of the "AF initiation algorithm" in CIED patients (NCT03357926).

Since my diploma thesis, I have been focussing my research on AF in patients receiving cardiac interventions. I created the transcatheter aortic valve implantation (TAVI) database at our institution together with my advisor. It evolved from the Austrian TAVI Registry, which served as my diploma thesis topic. The main research questions were

a) the effect of pre-existing AF on the outcome after TAVI,

b) the incidence of new-onset AF after TAVI and

c) the effect of new-onset AF on the long- and short-term outcome.

During the recent years it has been proposed that left atrial appendage closure (LAAC) limits the risk of stroke in AF patients who are not susceptible to oral anticoagulation. As

this method has just been evaluated a few years ago and is performed in Austria since 2010, there is still insufficient data about the risks and benefits of LAAC in daily clinical practice. I had the opportunity to contribute to the establishment of the Austrian LAAC registry (NCT03409159).

As this thesis describes only a part of my work during the doctoral study, all publications and posters originating from the doctoral study are listed in the Appendix.

Acknowledgement

I owe my sincere gratitude to my advisor Daniel Scherr for his continuous support of my preclinical and clinical research, for his patience, immense knowledge and motivation. His guidance is not limited to the dissertation and other matters of research; he also helped me starting my clinical career at the Division of Cardiology of Graz and its continuation in Vienna. I could not have imagined a better mentor!

Besides my advisor, I also would like to thank Peter Rainer and Günter Schreier for their insightful comments and encouragement during the development of my thesis.

My thank also goes to Martin Manninger, who is not only the colleague I learned the most from, but also has become a friend over the many years we worked together. Moreover, I especially want to thank my parents Robert Zweiker and Gudrun Zweiker, who did not only raise me, but also guided me through the jungle of clinical medicine before and after graduation. Furthermore, I would like to thank my colleagues Theresa Glantschnig, Johannes Gollmer, Ewald Kolesnik, Tanja Odeneg, Bernadette Pratl, Andreas Praschk, Albrecht Schmidt, Nicolas Verheyen (listed in alphabetical order), who supported me with continuous efforts to allow progress in the research projects that were important to me. Furthermore, I would like to thank Alessio Alogna, Michael Schwarzl and Heiner Post, who introduced me into scientific thinking and the basics of cardiovascular research at the very beginning of my career. I am also very grateful for the support by the current and former heads of the departments I currently work at (Andreas Zirlik, Kurt Huber, Burkert Pieske and Helmut Brussee).

Finally, I would especially thank my wife, Hanna, and my daughter, Dana. Without you, I would not realize the most important things in life. Dana, your birth gave the last necessary push to finish my dissertation. Although you are only a few months old, you already have

become the biggest project of my life. I also thank the rest of my family for their love, support and constant encouragements, with special thanks to by brother Stefan, who regularly supports me with the preparation of manuscripts (like this thesis).

Abstract

This dissertation comprises of three different aspects of atrial fibrillation (AF) in the context of cardiovascular interventions and/or devices, addressing (1) the evaluation of an AF prediction algorithms in patients with cardiovascular implantable electronic devices (CIEDs), (2) the impact of AF on patients undergoing transcatheter aortic valve implantation (TAVI), and (3) left atrial appendage closure (LAAC) in AF patients who cannot receive oral anticoagulation (OAC).

Evaluation of an AF prediction algorithm

With evolving technology, current CIEDs are already able to document cardiac arrhythmias. They detect atrial high rate episodes which can precede for AF and are associated with elevated stroke risk. Since there are many indications for implantable pacemakers and implantable cardioverter defibrillators, patients with CIEDs may serve as ideal population for studying the efficacy of AF prediction algorithms. In cooperation with our institution, Hayn et al. of the Austrian Institute of Technology (AIT) developed an algorithm to predict the probability of future AF episodes from surface ECG. This "AF initiation algorithm" assesses P wave morphology features of premature supraventricular beats and compares it to "regular" P waves. To allow further development of the algorithm, we initiated a prospective study including patients with CIEDs.

AF and TAVI

AF influences the outcome of structural cardiac interventions, and vice versa. For example, transcatheter aortic valve implantation has emerged as an alternative to conservative treatment in in operable high-risk patients and to conventional surgical aortic valve replacement in intermediate risk patients. Pre-existing AF has been shown to worsen the

outcome after TAVI and is therefore included in recent risk evaluation scores. However, while AF may newly develop after TAVI, there is conflicting evidence of the effect of new-onset AF on long-term outcome. A retrospective study of TAVI patients at our centre significantly improved the understanding of the association between new-onset AF and outcome after TAVI.

Non-pharmacological stroke prevention in AF patients

Some patients are not suitable to receive OAC due to elevated bleeding risk. LAAC has been developed in recent years as an option for those patients and has been shown to be non-inferior to traditional OAC therapy. A national registry has been established to assess the efficacy and safety of LAAC in daily clinical practice.

With my dissertation, I aimed at contributing to a better understanding of AF from its diagnosis, to its outcome and therapy. I describe the frequency of AF, difficulties in the diagnostic pathway, its effect on outcome after cardiac interventions, and invasive interventions to prevent further complications.

Zusammenfassung

Diese Dissertation behandelt verschiedene Aspekte von Vorhofflimmern (VHF) in Zusammenhang mit kardialen Prozeduren, nämlich (1) die prospektive Evaluierung eines VHF-Vorhersage-Algorithmus bei Patienten mit kardiovaskulären implantierbaren elektronischen Geräten, (2) den Einfluss von Vorhofflimmern auf Patienten, die sich einer Transkatheter-Aortenklappen-Implantation (TAVI) unterziehen und (3) das Outcome nach interventionellem Herzohrverschluss bei VHF-Patienten, bei denen eine orale Antikoagulation kontraindiziert ist.

Evaluation eines VHF-Vorhersage-Algorithmus

Heutzutage können kardiovaskuläre implantierbare elektronische Geräte (z.B. Schrittmacher, implantierbare Defibrillatoren), Rhythmusstörungen von einer Dauer von nur wenigen Sekunden aufzeichnen. Atriale Hochfrequenzepisoden, die Vorboten von VHF sein können, werden ebenfalls aufgezeichnet. Diesen Vorteil macht sich das SAFE-ME Projekt zunutze, das in einer Patientenpopulation mit kardiovaskulärem implantierbarem elektronischem Gerät die Effektivität eines VHF-Prädiktions-Algorithmus überprüft. In Zusammenarbeit mit unserer Abteilung entwickelte das AIT (Austrian Institute of Technology) einen Algorithmus, um die Wahrscheinlichkeit für das Auftreten von VHF innerhalb der nächsten Stunden, Wochen oder auch innerhalb des nächsten Jahres vorhersagen kann. Dieser Algorithmus überprüft die P-Wellen-Morphologie von supraventrikulären Extrasystolen und vergleicht sie mit „normalen“ P-Wellen. Im SAFE-ME Projekt wird der Algorithmus erstmals anhand einer prospektiven Population mit Schrittmacher oder Defibrillator überprüft.

VHF und TAVI

In mehreren Studien zeigte sich bereits ein gegenseitiger Einfluss von Vorhofflimmern strukturellen Interventionen in der Kardiologie. Ein Beispiel ist die TAVI, die sich mittlerweile als gute Alternative zum konventionellen chirurgischen Aortenklappenersatz etabliert hat. Vorbestehendes Vorhofflimmern hat nachweislich einen negativen Einfluss auf das Outcome nach TAVI und ist derzeit als Risikofaktor in aktuellen Risiko-Scores enthalten. Vorhofflimmern entsteht oft auch während der Prozedur, und es gibt derzeit keine klaren Daten über den Einfluss dieser Rhythmusstörung auf den weiteren klinischen Verlauf. Eine retrospektive Analyse in unserem Zentrum untersuchte den Einfluss von neu aufgetretenem Vorhofflimmern auf klinische Parameter nach der TAVI.

Nicht-medikamentöse Schlaganfallprävention in VHF-Patienten

Bei einem Teil der VHF-Patientenpopulation ist eine herkömmliche Antikoagulation aufgrund einer erhöhten Blutungsrisikos oder mangels Effektivität nicht sinnvoll. Um das Schlaganfallrisiko hintanzuhalten, wurde in den letzten Jahren der interventionelle Herzohrverschluss als Alternative entwickelt. Ein nationales Register wurde in Österreich etabliert, um die Effektivität und Sicherheit des interventionellen Herzohrverschlusses im klinischen Alltag zu überprüfen.

Zusammenfassend versuche ich mit meiner Dissertation etwas zum Verständnis von VHF beizutragen, nämlich sowohl in der Diagnostik als auch in der Therapie. Ich zeige die Häufigkeit von VHF auf, sowie Schwierigkeiten bei der Erkennung, seine Auswirkungen auf kardiale Eingriffe und eine neue Intervention um Komplikationen in ausgewählten Fällen abzuwenden.

Table of contents

Preface iv

Acknowledgement vi

Abstract viii

Zusammenfassung x

List of Abbreviations xvii

List of Figures xix

List of Tables xxi

1 Atrial fibrillation 1

1.1 Definition 2

1.2 Clinical diagnosis and classifications 3

1.2.1 Stroke risk 4

1.2.2 Symptom severity 5

1.2.3 Severity of AF burden 6

1.2.4 *Subclinical* AF, atrial high rate event (AHRE) 7

1.2.5 Pre-existing and new-onset AF 7

1.2.6 *Terminology to be abandoned* 8

1.3 Pathophysiology 9

1.3.1 Structural remodelling 10
1.3.2 Electrical remodelling 10
1.4 Symptoms and complications 11
1.4.1 Cardioembolic stroke 11
1.4.2 Direct symptoms of AF 14
1.4.3 Heart failure 15
1.5 Treatment (ABC pathway) 16
1.5.1 Anticoagulation / Avoid stroke 16
1.5.2 Better symptom control 19
1.5.3 Comorbidities / Cardiovascular risk factor management 22
1.6 Screening for AF 24
1.6.1 Indirect signs of AF 24
1.6.2 Long-term ECG documentation 24
1.6.3 Photoplethysmography for AF screening 24
2 Introduction to subtopics 26
2.1 AF prediction 27
2.1.1 ECG algorithms 27
2.2 AF and TAVI 29
2.2.1 Aortic stenosis (AS) 29

2.2.2 Surgical aortic valve replacement 32
2.2.3 Balloon valvuloplasty 33
2.2.4 TAVI 33
2.2.5 AF and AS 34
2.2.6 NOAF 35
2.3 AF and non-medicinal stroke prevention 36
2.3.1 LAAC 36
3 Studies 40
3.1 Research questions 41
3.1.1 AF prediction 41
3.1.2 AF and TAVI 41
3.1.3 Austrian LAAC Registry 41
3.2 SAFE-ME study 43
3.2.1 Methods 43
3.2.2 Results 49
3.3 AF-TAVI study 59
3.3.1 Methods 59
3.3.2 Results 60
3.4 Austrian LAAC Registry 77

3.4.1 Methods 77

3.4.2 Results 80

4 Discussion 99

4.1 AF prediction and the SAFE-ME study 100

4.1.1 Incidence of AHRE 100

4.1.2 Predictors of AHRE 100

4.1.3 Limitations 101

4.1.4 Outlook 101

4.2 AF, TAVI and the AF-TAVI study 103

4.2.1 Patient cohort 103

4.2.2 Risk scores for TAVI patients 104

4.2.3 Predictors of mortality 104

4.2.4 NOAF 105

4.2.5 Limitations 106

4.2.6 Summary of other TAVI-related studies 107

4.3 AF, non-medicinal stroke prevention and the Austrian LAAC registry 108

4.3.1 Indications for LAAC 108

4.3.2 Procedural outcome 109

4.3.3 Post-procedural antithrombotic treatment 110

4.3.4 Long-term outcome 111

4.3.5 Limitations 112

4.3.6 Outlook 113

5 Conclusion 114

6 Summary and perspectives 115

References 116

Appendix 139

Publications originating from the doctoral study 140

Main papers 140

Other papers 140

Abstracts 142

Copyright notice 145

CRF of the SAFE-ME study 146

List of Abbreviations

AF	Atrial fibrillation
AHRE	Atrial high rate episode
AS	Aortic stenosis
AIT	AIT Austrian Institute of Technology
CIED	Cardiovascular implantable electronic device
DOAC	Direct oral anticoagulant
EAPCI	European Association of Percutaneous Cardiovascular Interventions
ECG	Electrocardiogram
EHRA	European Heart Rhythm Association
ESC	European Society of Cardiology
ESUS	Embolic stroke of unknown source
FDA	Federal Drug Administration
IEGM	Intracardiac electrogram
ICD	Implantable cardioverter-defibrillator
ICE	Intracardiac echocardiography
INR	International Normalized Ratio
IQR	Interquartile range

LAA	Left atrial appendage
LAAC	Left atrial appendage closure
NOAC	Non-VKA oral anticoagulant
NOAF	New-onset AF
OAC	Oral anticoagulation
PAF	Paroxysmal AF
PV	Pulmonary vein
SAVR	Surgical aortic valve replacement
TAVI	Transcatheter aortic valve implantation
TOE	Transoesophageal echocardiography
VKA	Vitamin K antagonist

List of Figures

Figure 1. Atrial excitation in sinus rhythm and atrial fibrillation. 1A: In normal sinus rhythm, activation of the sinus node is propagated to both atria and through the AV node into the ventricles in a regular manner. 1B: In atrial fibrillation, atrial excitation is unsynchronized and irregular. This leads to fast conduction to the AV node followed by irregular excitation of the ventricles. LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle; AV: atrioventricular. 2

Figure 2. This example ECG shows AF: Absolutely irregular RR intervals and no discernible, distinct P waves. RR intervals are displayed. AF: atrial fibrillation, ECG: electrocardiogram. 3

Figure 3. The “CC To ABC” scheme. AF: atrial fibrillation; ECG: electrocardiography. Adapted from (1). 4

Figure 4. Major mechanisms causing atrial fibrillation. Various pathophysiological factors cause complex changes in the myocardium of both atria, which promote AF. Furthermore, AF facilitates itself. AF may lead to stroke and heart failure. Adapted from (3). 9

Figure 5. Two-chamber view of the heart during sinus rhythm and thrombus formation during AF. While atrial contractions during SR lead to regular blood flow in the LAA, the functional arrest of the atria during AF promotes haemostasis and thrombus formation in the LAA. AF: atrial fibrillation; LA: left atrium; LAA: left atrial appendage; LV: left ventricle. 12

Figure 6. Schematic view of the apical 5-chamber view of the heart (A) and changes in AS (B). AS: aortic stenosis; AV: aortic valve; LA: left atrium; LV: left ventricle; MV: mitral valve; RA: right atrium; RV: right ventricle. Please see text for further abbreviations. 29

Figure 7. Natural progression of AS. After a long asymptomatic period with normal life span, survival declines dramatically after onset of symptoms. AS: aortic stenosis. Based on (85). 31

Figure 8. Schematic figure of different strategies of access for TAVI and the TAVI procedure itself. TAVI: transcatheter aortic valve implantation. 34

Figure 9. Principle of endocardial (A) and epicardial (B) LAAC devices. LAAC: left atrial appendage closure..... 36

Figure 10. Endocardial access of the LAA by transseptal puncture. LA: left atrium; LAA: left atrial appendage; LV: left ventricle; RA: right atrium; RV: right ventricle; VCI: vena cava inferior. 37

Figure 11. Study plan of the SAFE-ME study. AF: atrial fibrillation. ECG: electrocardiogram. ICD: implantable cardioverter-defibrillator, PM: pacemaker. 45

Figure 12. Anticipated timeline of the SAFE-ME study. 48

Figure 13. Flow chart of this interim analysis of the SAFE-ME study. 51

Figure 14. Study flowchart. LAAC: left atrial appendage closure. 80

Figure 15. Indications for LAAC. LAAC: left atrial appendage closure. 86

Figure 16. Kaplan Meier plot of cumulative survival of patients after LAAC, stratified by subgroup. LAAC: left atrial appendage closure. 96

List of Tables

Table 1. CHA_2DS_2-VASc score. Based on data from (6). 5

Table 2. Modified EHRA score. AF: Atrial fibrillation. EHRA: European Heart Rhythm Association. 6

Table 3. Modifiable and non-modifiable bleeding risk factors adapted from (1). Marked risk factors (*) are considered “potentially” modifiable. 18

Table 4. classification of AS, adapted from (82, 88). 32

Table 5. Baseline characteristics of all included patients, AHRE group and no-AHRE group. AF: atrial fibrillation; AHRE: atrial high rate episode. 52

Table 6. Device details of included patients. AV: atrioventricular; CRT: cardiac resynchronization therapy; AHRE: atrial high rate episode; nsVT: non-sustained ventricular tachycardia. 56

Table 7. Baseline characteristics of treated patients. 62

Table 8. Intrahospital complications, length of stay and time-dependent mortality of treated patients. 71

Table 9. Out-of-hospital outcome and composite endpoints. 74

Table 10. Univariable and multivariable analyses. 76

Table 11. Baseline characteristics of treated patients grouped by indication for LAAC. LAAC: left atrial appendage closure. 81

Table 12. Procedural outcome and follow-up echocardiography. 89

Table 13. Post-procedural anticoagulation strategy. DAPT: double antiplatelet therapy, DOAC: direct oral anticoagulant, LMWH: low molecular-weight heparin, SAPT: single antiplatelet therapy, VKA: vitamin K antagonist. 93

Table 14. Follow up after LAAC. LAAC: left atrial appendage closure. Reproduced from Zweiker et al (116) licensed under CC BY. 97

Table 15. Mean predicted annual stroke and bleeding events (as by CHA_2DS_2-VASc and HAS-BLED scores) compared to reported events in the Austrian LAAC Registry. LAAC: left atrial appendage closure. Reproduced from Zweiker et al (116) licensed under CC BY. 98

1 Atrial fibrillation

1.1 Definition

Atrial fibrillation (AF) is an abnormal heart rhythm, defined as irregular, rapid and unsynchronized activation of the atrial tissue and consequently ineffective atrial contraction (Figure 1) (1). With a prevalence of 3% in adults aged 20 years or older, it is the most common relevant arrhythmia worldwide (2, 3). AF is associated with a two-fold and 1.5-fold increased risk of all-cause mortality in women and men, respectively. It is also associated with increased morbidity, especially heart failure and stroke. As a result, 10–40% of AF patients have to be hospitalized each year (1).

While acute heart failure and sudden cardiac death may occur in AF patients even at best medical care, cardioembolic stroke and its serious consequences can almost entirely be prevented with adequate anticoagulant medication (1). Since every fifth stroke occurs due to AF (4) and cardioembolic strokes are more severe than those of other causes (5), the detection and treatment of AF is of major interest in health systems globally.

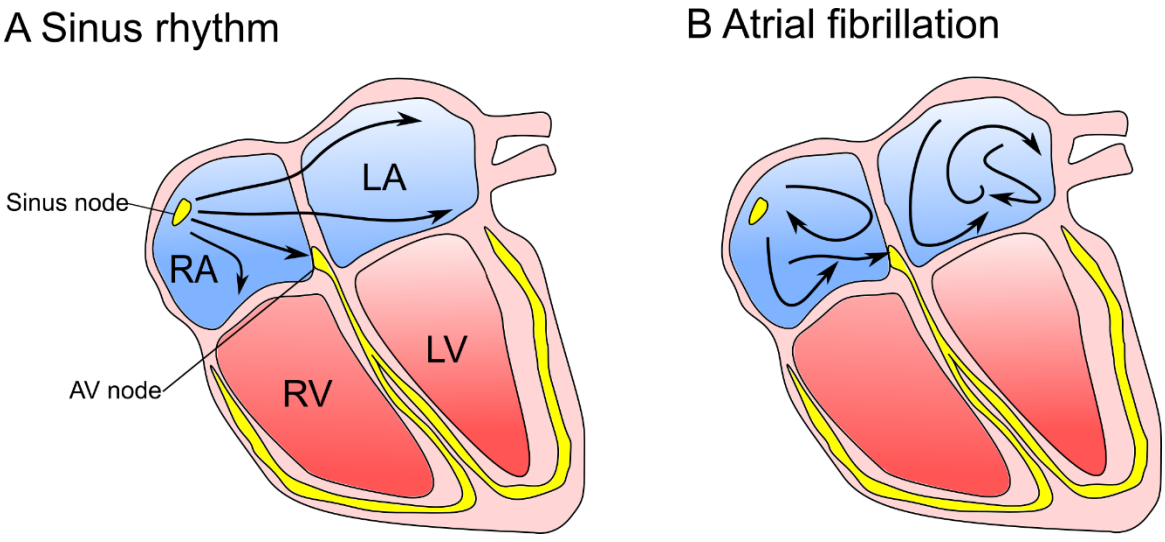


Figure 1. Atrial excitation in sinus rhythm and atrial fibrillation. 1A: In normal sinus rhythm, activation of the sinus node is propagated to both atria and through the AV node into the ventricles in a regular manner. 1B: In atrial fibrillation, atrial excitation is unsynchronized and irregular. This leads to fast conduction to the AV node followed by irregular excitation of the ventricles. LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle; AV: atrioventricular.

1.2 Clinical diagnosis and classifications

For the clinical diagnosis of AF, rhythm documentation using either a single-lead ECG recording with a minimum duration of 30 seconds or a standard 12-lead ECG is required (1). Typical characteristics include 1) “irregularly irregular R-R intervals” (1) (when there is no atrioventricular block), 2) no discernible, distinct P waves, and 3) irregular atrial activations. An example ECG is shown in Figure 2.

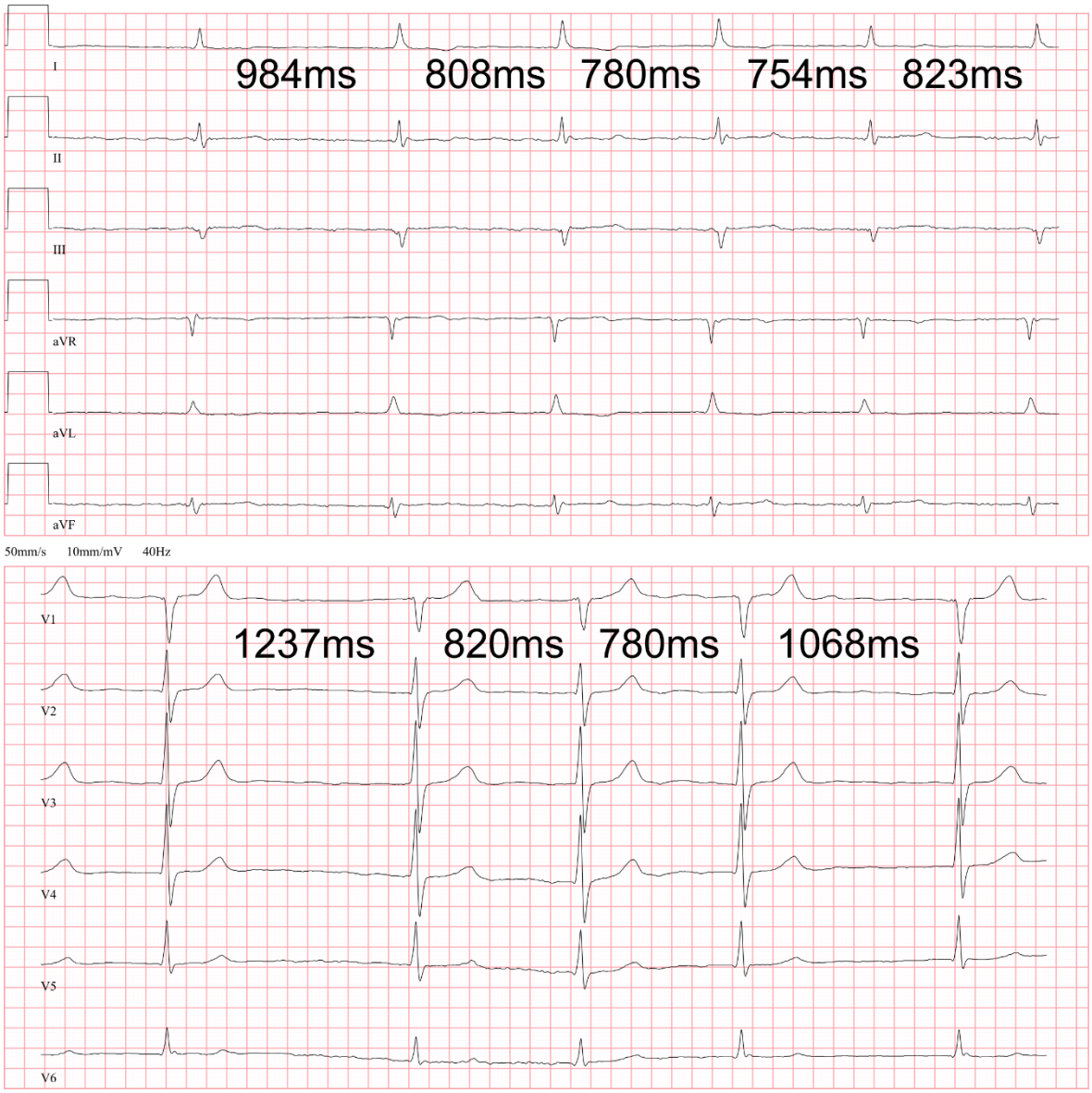


Figure 2. This example ECG shows AF: Absolutely irregular RR intervals and no discernible, distinct P waves. RR intervals are displayed. AF: atrial fibrillation, ECG: electrocardiogram.

The European Society of Cardiology (ESC) guidelines for the diagnosis and management of AF endorse the "CC To ABC" pathway to adequately characterize and treat AF (1). Once AF has been confirmed (first "C") by ECG, it should be characterized (second "C") using the "4S-AF scheme" and treated using the "ABC" pathway (Figure 3).

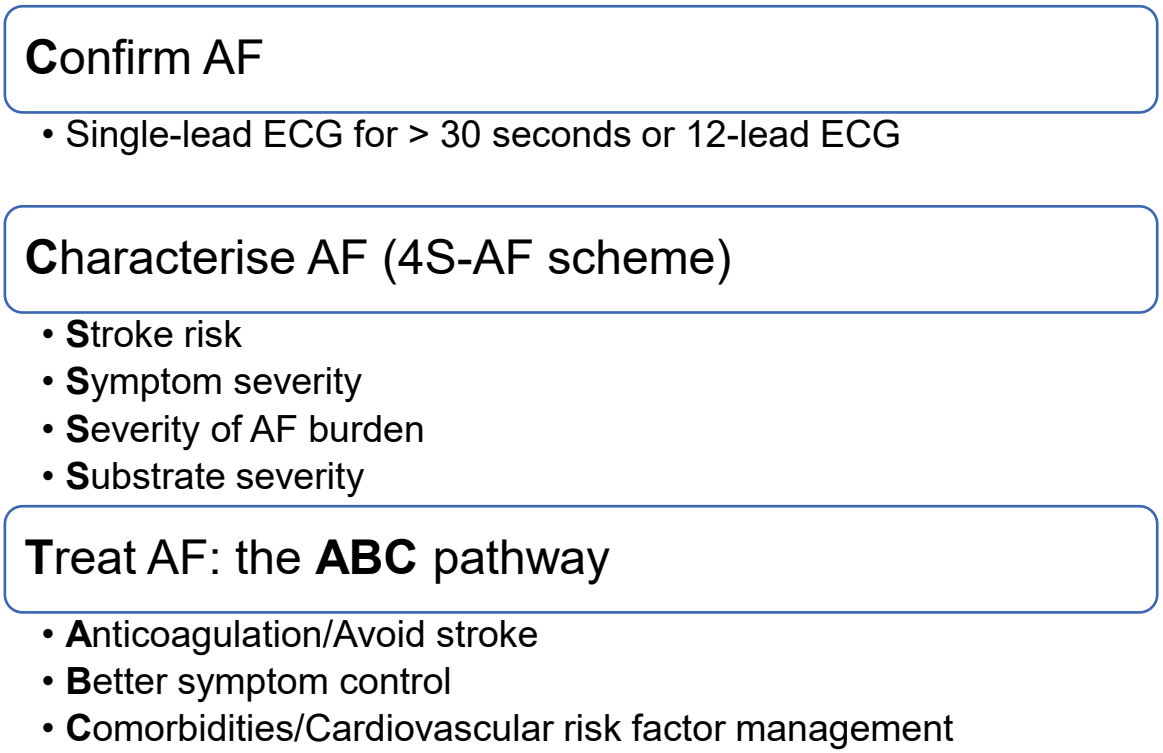


Figure 3. The "CC To ABC" scheme. AF: atrial fibrillation; ECG: electrocardiography. Adapted from (1).

1.2.1 Stroke risk

AF leads to increased risk of thromboembolism, above all cardioembolic stroke, in most patients. This risk has been shown to be dependent on further comorbidities, age and gender. To identify patients with increased risk and indication for stroke prevention therapy, the CHA_2DS_2-VASc (Table 1) score has been introduced (6).

risk factor	points
c*ongestive heart failure*: The presence, signs and symptoms of either right or left ventricular failure, or both, confirmed by non-	1

invasive or invasive measurements demonstrating objective evidence of cardiac dysfunction	
*arterial **h**ypertension*: A resting blood pressure > 140 mmHg systolic and/or > 90 mmHg diastolic on at least 2 occasions or currently on antihypertensive treatment	1
***a**ge ≥ 75 years*	2
***d**iabetes*: Fasting plasma glucose ≥ 126 mg/dL or treatment with oral antidiabetic agents and/or insulin	1
***s**troke, TIA or thromboembolism*: Focal neurologic deficit of sudden onset as diagnosed by a neurologist and caused by ischemia, lasting > 24 hours (stroke) or < 24 hours (TIA). Thromboembolism was either pulmonary, cerebral peripheral.	2
***v**ascular disease*: prior myocardial infarction, peripheral artery disease or aortic plaque	1
***a**ge 65-74 years*	1
***s**ex **c**ategory (female gender)*	1

Table 1. CHA_2DS_2-VASc score. Based on data from (6).

1.2.2 Symptom severity

The ESC recommends to use the modified EHRA symptom scale for classification of symptoms of AF in daily clinical practice and research (Table 2) (1).

Modified EHRA score	Symptoms	Description

1	None	AF is asymptomatic.
2a	Mild	The normal daily activity is not affected.
2b	Moderate	The normal daily activity is not affected, but the patient is troubled by symptoms.
3	Severe	The normal daily activity is affected.
4	Disabling	The normal daily activity is discontinued.

Table 2. Modified EHRA score. AF: Atrial fibrillation. EHRA: European Heart Rhythm Association.

1.2.2.1 Silent AF

In a significant proportion of patients, AF does not lead to any symptoms, which should be called *asymptomatic AF*. Unfortunately, those patients may have delayed treatment and, therefore, are subject to a higher risk of complications than symptomatic patients (7).

1.2.3 Severity of AF burden

AF should also be characterized by its burden (1). Even if the individual progression of AF varies from patient to patient, it normally follows these patterns from short, paroxysmal episodes to a finally permanent arrhythmia that is accepted by the patient.

- *First diagnosed AF*: If AF is first diagnosed by ECG, regardless of previous signs and symptoms, it shall be called *first diagnosed AF*.

- *Paroxysmal AF*: At the beginning of the disease, patients often suffer from episodes of self-terminating AF. These *paroxysms* normally convert to SR within 24-48 hours, but they can last up to 7 days.

- *Persistent AF*: If episodes of AF persist even more than 7 days or do not convert to SR spontaneously at all (e.g., a pharmacological or electric intervention is required), AF is called *persistent*.

- *Long-standing persistent AF*: Persistent AF lasting at least one year is called *long-standing*, as long as there are still actions taken to treat the arrhythmia (i.e., *rhythm control*).

- *Permanent AF*: As soon as the arrhythmia is accepted by both the patient and the physician, it is called *permanent*. By definition, no further actions are taken to convert the arrhythmia to sinus rhythm.

1.2.4 *Subclinical* AF, atrial high rate event (AHRE)

The term "subclinical AF" was first introduced by Healey et al (8) and refers to atrial arrhythmias with an atrial rate of ≥ 175/min, which have not been documented by surface ECG. They are normally detected by cardiovascular implantable electronic devices (CIEDs), which provide an intracardiac electrogram (IEGM) instead of an ECG. Because the official definition of AF is not fulfilled (i.e., documentation by surface ECG) (1), it is also called *atrial high rate event* (AHRE) (9). This term will also be used throughout this thesis. AHREs have been associated with increased risk of stroke (8), but due to lacking evidence further treatment is currently not indicated in most cases (9).

1.2.5 Pre-existing and new-onset AF

When investigating the impact of a procedure on AF and/or vice-versa, the terms "pre-existing AF", and "new-onset AF" (NOAF) or "postoperative AF" are used. Pre-existing AF corresponds to a history of AF already before any intervention has been performed. New-onset/postoperative AF is defined as new diagnosis of AF after the procedure.

1.2.6 *Terminology to be abandoned*

Historically, patients with AF were stratified into *valvular* and *non-valvular* AF based on the presence of *rheumatic* mitral valve disease (especially mitral valve stenosis) or a mechanical heart valve. As patients with *valvular* AF are subject to a higher risk of thromboembolic complications, differences in the indication and type of treatment exist. To avoid any misclassification of patients with other types of valvular heart disease, the current guidelines do not endorse this nomenclature any more (1). The recent guidelines also abandon the term *Lone AF* (previously indicating absence of AF stroke risk factors) and *chronic AF*.

1.3 Pathophysiology

The exact pathways for the initiation of AF are currently not fully understood (1). The genetic predisposition has been shown to play an important role in the development of AF independently of concomitant cardiovascular factors (10). Many single nucleotide polymorphisms have already been identified and up to one-third of AF patients carry such common genetic variants (11). Especially AF in the absence of any cardiovascular risk factors is a condition with clustering in families (12). It is thought that such genetic variants could become useful in the future for patient selection of treatment or even specific therapies (1).

In addition to genetic factors, several external factors are present in the majority of patients before AF occurs. Those stressors of the atria and AF itself lead to both structural and electrical remodelling (Figure 4).

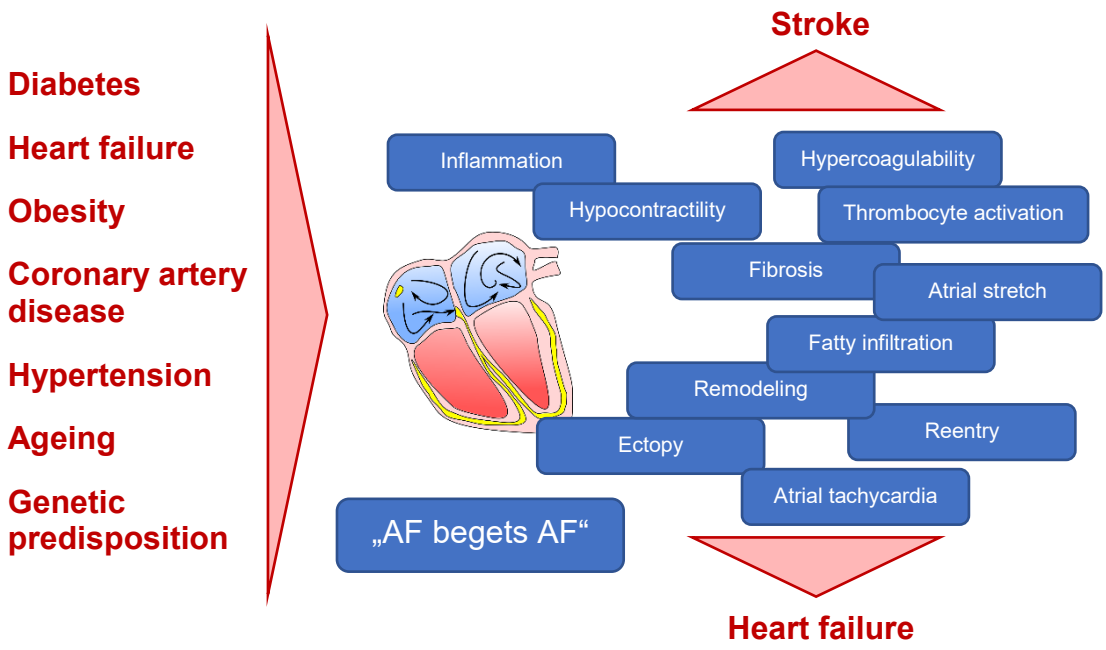


Figure 4. Major mechanisms causing atrial fibrillation. Various pathophysiological factors cause complex changes in the myocardium of both atria, which promote AF. Furthermore, AF facilitates itself. AF may lead to stroke and heart failure. Adapted from (3).

1.3.1 Structural remodelling

External stressors such as structural heart disease and hypertension, as well as AF itself, induce a slow but progressive process of structural remodelling in both atria. The myocardial tissue structure of both atria changes on a molecular, microscopic and a macroscopic level. Fibrosis, collagen incorporation and inflammatory infiltrates are major players in this process (1). Even in AF patients with normal atrium in terms of size, microscopic changes have been found (13). The inflammatory reaction of atrial tissue leads to activation of thrombogenic acute phase proteins (such as von Willebrand factor or interleukin 6) into the blood (14).

Furthermore, the atria react to increased pressure by macroscopic enlargement (15). This effect can stronger if more cardiovascular factors are present (16). Due to the change in conduction size of the atria, macroscopic structural remodelling favours the persistence of AF by re-entry circuits (17).

1.3.2 Electrical remodelling

During AF, atrial tissue reacts to rapid depolarizations and increased wall pressure by fundamental changes in atrial signalling (17). Oxidative stress and Ca^{2+} load increase and Ca^{2+}-dependent proteases are activated during AF. L-type Ca^{2+} channels and the repolarizing potassium current I_{to} have been shown to decrease, leading to a slowing of the first phase of atrial repolarization (18) and reduction of the action potential duration (APD) (17). The shortening of the atrial effective refractory period (AERP) is one of the cornerstones in electrical remodelling and allows a perpetuation of AF (“AF begets AF”) (19). However, in the presence of cardiovascular risk factors, AF may initiate and continue even without any evidence of electrical remodelling (16).

1.4 Symptoms and complications

AF may lead to three different spectra of symptoms and complications: stroke, palpitations (directly due to irregular heart rhythm) and heart failure. Furthermore, complications from comorbidities lead also to adverse events, which should therefore be addressed in every AF patient (1).

1.4.1 Cardioembolic stroke

First demonstrated in 1980ies (20), there is now overwhelming evidence showing a causal relationship between AF and cardioembolic stroke. Indeed, AF is now recognized as one of the most important risk factors for stroke (1). Stroke or systemic thromboembolism might be the first symptom of AF in patients with silent AF.

According to the triad of Virchow, coagulation is dependent in 1) blood flow, 2) endothelial or endocardial damage, and/or 3) coagulability of blood (21). All three factors play a major role in the promotion of cardiac thrombi in AF (22).

1.4.1.1 Hemodynamic stasis

Three factors lead to reduced blood flow in the atria. First, the loss of synchronized atrial contraction leads to deceleration of pulsatile blood flow through the atria. Second, atrial enlargement occurs due to an increase in atrial pressure. Third, total cardiac output is reduced due to a loss of atrial function. The result is blood stasis, which increases the possibility of thrombus formation (Figure 5).

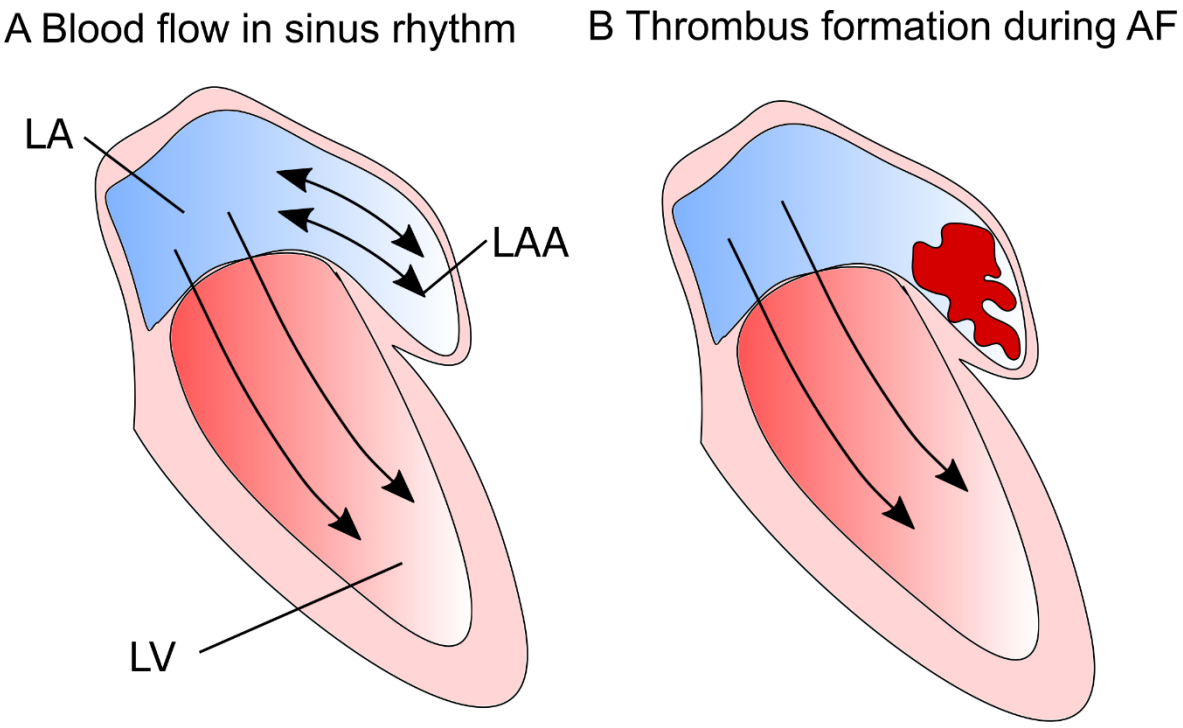


Figure 5. Two-chamber view of the heart during sinus rhythm and thrombus formation during AF. While atrial contractions during SR lead to regular blood flow in the LAA, the functional arrest of the atria during AF promotes haemostasis and thrombus formation in the LAA. AF: atrial fibrillation; LA: left atrium; LAA: left atrial appendage; LV: left ventricle.

A predilection site for thrombus formation is the left atrial appendage (LAA) (23), a trabecular evagination of the left atrium at the anterior free wall (24). The LAA was first identified as prothrombotic region in the 1940ies in patients suffering from mitral valve disease and the surgical obliteration of the LAA in such patients was first described by Madden et al. (25). Since the introduction of transoesophageal echocardiography (TOE) into clinical practice in the 1990ies, many studies showed a direct correlation between the presence of thrombus in the LAA and ischemic stroke (26, 27). Blackshear et al showed that atrial thrombi were located in the LAA in non-valvular AF in > 90% of cases (28).

1.4.1.2 Hypercoagulability

The inflammation processes in the atrial tissue have an impact on the body's coagulation system. Acute phase proteins are released into the circulation and proteinase-activated receptors are upregulated (29). As result, certain intravascular promoters of

thrombogenesis (e.g., prothrombin fragments and thrombin-antithrombin complexes) are more prevalent in patients with AF, leading to an imbalance of the blood's coagulation system and favouring thrombogenesis (14).

1.4.1.3 Endocardial dysfunction

The aforementioned structural remodeling[1] of the atrial tissue is associated with endothelial dysfunction. By release of interleukin 6 and von Willebrand factor, aggregation of thrombocytes and thrombus formation are facilitated (22).

1.4.1.4 Time dependency of thrombogenicity

As both endocardial dysfunction and hypercoagulability are mechanisms that develop over time, their effects last even for a couple of weeks after successful cardioversion from AF to sinus rhythm. Although restoration of sinus rhythm immediately leads to synchronized depolarisation of the atrial tissue, "atrial stunning" reduces the atrial function for 6-8 weeks (14). This explains the high stroke risk in paroxysmal AF or in the first 4 weeks after cardioversion (1).

Recent research suggests that all the aforementioned factors may not be dependent on the arrhythmia itself and AF may just be a symptom of underlying mechanisms, which are now summarized under the term *atrial cardiomyopathy* (30). The first hint of this theory comes from the ASSERT study, primarily designed to test atrial overdrive pacing to prevent AF in pacemaker patients (31). The authors describe that that AF lasting just over 6 minutes was associated with 2.5 times increased stroke risk (8). Surprisingly, the authors found no temporal correlation between the occurrence of AF and stroke (32), with some

[1] Section 1.3.1 (page 8)

first episodes of AF even occurring after the thromboembolic event. If further clinical trials confirm these findings, it may be reasonable to initiate antithrombotic treatment even in patients with atrial cardiomyopathy without any evidence of AF.

1.4.1.5 Other causes and clinical manifestations

There are three main sources that lead to cardioembolic stroke: cardio-embolism, atherothrombosis and small vessel disease (33). Due to differences in pathophysiology, the cardio-embolic stroke is very well distinguishable in terms of clinical appearance and cranial imaging. While atherothrombosis and small vessel disease often lead to small infarcts (lacunar strokes) that occur and sometimes slowly evolve over time, the cardio-embolic stroke leads to a sudden, often complete ischaemia of a territory (34). As a result, AF-associated strokes are usually severe (5).

1.4.1.6 Embolic stroke of unknown source

In patients suffering from an ischaemic stroke with signs of cardio-embolic origin without the presence of AF or other cardiac factors favouring embolism, the term *embolic stroke of unknown source* (ESUS) has evolved (34). In those patients, extensive screening with ECG monitoring for at least 72 hours is indicated (1). Recent studies evaluated the use of oral anticoagulation (OAC) in ESUS patients even without the evidence of AF, but they found no benefit over aspirin (35, 36).

1.4.2 Direct symptoms of AF

Approximately 60% of patients experience symptoms during episodes of AF. These are more prevalent in female patients and may range from fear/anxiety and fatigue to palpitations, chest pain and dyspnoea (7). Paroxysmal episodes of AF are more often associated with symptoms compared with permanent AF (37). Interestingly, symptoms of

AF are inversely correlated with outcome as asymptomatic AF patients face a higher probability of stroke and death (7). A possible explanation is that symptomatic AF patients more often seek medical attention and therefore are treated appropriately.

1.4.3 Heart failure

AF may lead to or aggravate heart failure due to a loss of atrial contractility and a rapid ventricular conduction.

The left atrium is responsible for 10-20% of left-ventricular end-diastolic filling and pressure; at exercise, this proportion increases to 20-30% (38). As atrial depolarizations are unsynchronized in AF, the atrium is functionally inactive and does not participate hemodynamically in cardiac work. The effect of reduced cardiac output in AF compared to sinus rhythm is most pronounced in patients who already suffer from a reduced ventricular function (39).

Furthermore, AF normally leads to fast, irregular ventricular contractions. Increased heart rate may deteriorate the ventricular function by itself. This so-called tachycardia-induced cardiomyopathy (40) was one of the first acknowledged symptoms of AF and first described in 1913 (41). While it may lead to a severe reduction of left-ventricular function, it is reversible (42).

In patients with pre-existing heart failure, increased heart rate even within the normal range is associated with increased cardiovascular morbidity and mortality (43). Paroxysms of AF with fast ventricular conduction may lead to haemodynamic instability in this population. The control of heart rate is difficult in paroxysmal AF and specific therapies to reduce the heart rate on an atrial level (such as ivabradine (44)) are ineffective.

1.5 Treatment (ABC pathway)

The three cornerstones of AF treatment are summarized in the ABC pathway in the ESC guidelines (Figure 3):

- **A**nticoagulation/**A**void stroke
- **B**etter symptom control, and
- **C**omorbidities/**C**ardiovascular risk factor management.

This pathway has been shown to reduce adverse events compared to usual care in the randomized mAFA-II study (45).

1.5.1 Anticoagulation / Avoid stroke

The current guidelines recommend starting anticoagulation in all patients, except for those without risk factors. The most clinically relevant risk factors are summarized in the CHA_2DS_2-VASc score (Table 1). The female gender, however, has to be interpreted as a *risk modifier* rather than a *risk factor* (1).

There is consensus that patients with two risk *factors* are of elevated risk of stroke requiring preventive therapy. If one factor is present (i.e., CHA_2DS_2-VASc of 1 for men and 2 or women), current ESC guidelines recommend the initiation of antithrombotic therapy based on the assessment of individual stroke and bleeding risk, and the patient's preference.

1.5.1.1 Antithrombotic therapy

As the plasmatic coagulation plays a more important role in thrombus formation than platelet aggregation in AF (46), anticoagulants have superior effects in stroke prevention (1) compared to antiplatelets, with similar bleeding risk (47). In daily clinical practice,

three different anticoagulant drugs are in use: Vitamin K antagonists (VKA), low molecular weight heparin (LMWH), and direct oral anticoagulants (DOACs).

- *VKA*: Vitamin K antagonists (warfarin, phenprocoumon, acecoumarin) are in use since the 1950ies (48). They interfere with the coagulation cascade by inhibiting the enzyme *vitamin K epoxide reductase*, which normally activates vitamin K, which in turn activates coagulation factors II, VII, IX, X, as well as proteins S, C, and Z (49). VKAs were the standard of care for stroke prevention in AF until the introduction of DOACs (1). The advantage of VKAs is the overwhelming clinical experience. Furthermore, they are still the only treatment option for patients with rheumatic mitral valve disease or a mechanical valve. However, their physiologic effect depends on different factors, such as nutrition and liver function, and must therefore be monitored regularly by lab testing. The goal value International Normalized Ratio (INR) target range depends on the indication and is normally between 2 and 3.5.

- *LMWH*: Low molecular weight heparins (enoxaparin, nadroparin, dalteparin, tinzaparin) are subcutaneously-administered drugs and affect factors IIa, IXa, Xa, XIa, and XIIa. They normally require no regular drug monitoring. As long as adequate dosing (by body weight) is guaranteed, LMWHs establish a safe and effective antithrombotic effect (49). The main disadvantage is the necessity of two subcutaneous injections daily, which may also reduce adherence.

- *DOAC*: Direct oral anticoagulants, also known as non-VKA oral anticoagulants (NOACs), summarize recently developed orally-administered drugs, which either inhibit the factor Xa (rivaroxaban, apixaban, edoxaban) or factor II (dabigatran). Those medications combine the predictive action of LMWHs with convenient oral

intake. In phase III studies, DOACs showed at least non-inferiority compared to VKAs in both, stroke prevention and bleeding rates (50-53). The net clinical outcome is in favour of NOAC therapy with some limitations in chronic kidney disease. Therefore, they are now recommended at first-line therapy in patients with AF planned for anticoagulation (1).

Before starting anticoagulation therapy, the evaluation of bleeding risk is recommended, as all anticoagulants expose an increased risk of bleeding. Especially modifiable bleeding risk factors should be screened and treated adequately (Table 3). However, studies have shown that most patients benefit from oral anticoagulation, even in the presence of bleeding risk factors (54).

modifiable risk factors	**non-modifiable bleeding risk factors**
hypertension	age (≥ 65 years)
labile INRs	history of major bleeding
other medication predisposing to bleeding	previous stroke
excess alcohol (≥ drinks per week)	dialysis-dependent kidney disease or renal transplant
anaemia*	cirrhotic liver disease
impaired renal function*	malignancy
impaired liver function*	genetic factors
reduced platelet count or function*	biomarkers: High-sensitivity troponin, Growth differentiation factor 15

Table 3. Modifiable and non-modifiable bleeding risk factors adapted from (1). Marked risk factors (*) are considered "potentially" modifiable.

1.5.1.2 Non-medicinal therapy

In several patients, oral anticoagulation cannot be initiated, since they have a history of spontaneous severe bleeding (e.g., intracranial) or other contraindications. Furthermore, some patients suffer from repetitive thromboembolic events under anticoagulation despite exclusion of reversible causes (such as patent foramen ovale). It has been proposed to exclude of the LAA, which has been identified as predilection site for atrial thrombi in AF patients. However, the surgical LAA obliteration is associated with a high procedural risk if performed as stand-alone procedure, even though it has been safely performed during heart surgery for many decades. In the last two decades, new technologies emerged to exclude or close the LAA via either the endovascular or the epicardial access (23). The so-called left atrial appendage closure (LAAC) is a promising therapy, but further data is needed to adequately assess the operational area in which patients benefit most from this intervention. Results of the LAAC experience in Austria can be found at Chapter 3.4 (page 77).

1.5.2 Better symptom control

1.5.2.1 Rate control

AF normally leads to fast, irregular ventricular rhythm. According to current guidelines, rate control is the first-line therapy of AF to prevent symptoms and complications (1). Pharmacological rate control is sufficient in most patients. First line drugs are beta blockers (e.g., bisoprolol, carvedilol, metoprolol, nebivolol and esmolol), calcium channel blockers (e.g., diltiazem and verapamil), cardiac glycosides (e.g., digoxin and digitoxin). In heart-failure patients with reduced ejection fraction, beta blockers are recommended as first line therapy, while a recent open-label study suggests superiority of digoxin (55). Ultimately, amiodarone may be used. (1)

If a high ventricular rate cannot be lowered pharmacologically, an ablation of the atrioventricular node with the requirement for permanent pacemaker therapy ("ablate and pace") remains as a last option.

1.5.2.2 Rhythm control

In every AF patient with symptoms persisting despite rate control, a rhythm control strategy is generally indicated. If the AF episode had only lasted < 12 hours, it may be reasonable to delay cardioversion as episodes of paroxysmal AF normally resolve within 24 hours (1, 56).

Thromboembolic risk is significantly higher during and after the conversion from a longer episode of AF (> 12 hours) to SR (57). Consequently, the risk of a pre-existing left atrial thrombus should be minimized beforehand. These patients should therefore either receive adequate anticoagulation for at least three weeks before cardioversion, or the presence of thrombi should be excluded TOE, if the arrhythmia may have persisted over 48 hours. The OAC should then be continued for at least 4 weeks (1).

According to the severity of symptoms, duration of AF and comorbidities, three different rhythm control strategies can be pursued:

1.5.2.3 Electric cardioversion

Electric cardioversion for treatment of AF is the first line therapy for recent onset AF with acute heart failure (1), but also very effective in short-standing persistent AF. The main advantage is the short half-life of a few milliseconds. As an electric shock is very painful, it is usually performed in sedative analgesia. If the electric cardioversion is not successful at first attempt, pharmacological antiarrhythmic therapy could be added before further attempts.

1.5.2.4 Antiarrhythmic drug therapy

For acute medicinal cardioversion, a few different antiarrhythmic medications are available, but contraindications have to be considered. In most patients with significant heart disease, intravenous amiodarone is the drug of choice. If structural heart disease is excluded, flecainide, propafenone, vernakalant, and ibutilide can be administered intravenously. In patients with good haemodynamic tolerance to paroxysmal AF episodes, a "pill in the pocket" (e.g., flecainide or propafenone) can be considered for patient-led cardioversion.

If recurrent symptomatic AF episodes emerge, a chronic antiarrhythmic therapy should be initiated, using dronedarone, flecainide or propafenone. If these antiarrhythmic drugs are ineffective or contraindicated (especially in co-existing cardiac disease), amiodarone may be effective, but side effects have to be kept in mind. (1)

1.5.2.5 Surgical procedures

Already in the early 1980ies, many different procedures have been developed to electrically isolate specific regions of the atrium, which are especially vulnerable to develop AF, by incisions. The *Maze procedure*, developed by James Cox, avoids macro re-entry by creating an electrical maze in the atria and excludes predilection sites for AF initiation (i.e., the pulmonary veins, the LAA and the right atrial appendix). In the first reports, high success rate was documented (58). According to current guidelines, the Maze procedure may be considered in AF patients undergoing heart surgery (recommendation level IIa, level of evidence A (1)).

1.5.2.6 Interventional procedures

An effective alternative or add-on to antiarrhythmic drug therapy is cardiac ablation for AF. As Haissaguerre et al found the pulmonary veins (PVs) as frequent initiation areas of AF (59), the isolation of all PVs has become the cornerstone of AF ablation therapy (60). Furthermore, other ablation techniques (such as ablation of the cavotricuspid isthmus, other linear lesions and non-PV triggers, such as rotors and complex fractionated atrial electrograms) have been developed, but do not seem to be as effective as PV ablation (60).

AF ablation has been shown to reduce AF burden and symptoms during AF episodes (61), and it is therefore recommended as first-line therapy in paroxysmal AF (class IIa) and second-line therapy after failure of antiarrhythmic drug therapy (class I). Furthermore, the ESC guidelines recommend AF ablation to improve cardiovascular outcome in heart failure patients as recent data suggest reduced mortality and hospitalizations in this patient population (62).

1.5.3 Comorbidities / Cardiovascular risk factor management

The optimal treatment of cardiovascular comorbidities and risk factors represents the third cornerstone in "ABC pathway". It has been shown to improve the maintenance of sinus rhythm in patients with persistent AF (63).

1.5.3.1 Lifestyle interventions

In obese patients, weight loss together with the management of other risk factors has been shown to reduce AF burden and is therefore recommended. Alcohol excesses should be avoided as they represent a risk factor for incident AF. Moderate physical activity should be undertaken; however, chronic excessive endurance exercise may promote AF progression (1).

1.5.3.2 Control of comorbidities

Obstructive sleep apnoea syndrome, arterial hypertension and diabetes mellitus represent partly modifiable risk factors for the development of AF (1). Therefore, their control is crucial to reduce AF burden. Furthermore, AF patients should have well-controlled blood pressure, as intracranial bleeding due severe hypertension may be complicated by the antithrombotic effects of OAC.

1.6 Screening for AF

As silent AF is associated with increased risk of cardiovascular events and mortality (7), screening for AF is of increased importance in special patient populations.

1.6.1 Indirect signs of AF

Certain ECG changes have been shown to be associated with increased risk for AF in the past or future. These include a high number of supraventricular premature beats, changes in the axes of P waves. In the last years, ECG algorithms have been evaluated but currently do not present daily clinical practice.

Other adjunct parameters may further improve specificity and sensitivity of ECG signs: left atrial size, CHA_2DS_2-VASc score and biomarkers (64).

Although AHREs clearly violate the definition of AF, it is a matter of debate if they may be treated with OAC. Even if patients with AHRE are of elevated risk for AF, in the majority of cases they will not develop AF in their further life (65).

1.6.2 Long-term ECG documentation

To increase the sensitivity of ECG, the duration of acquisition can be prolonged. Usually, 24-hour or 7-day Holter ECG monitoring belong to the diagnostic workup if there is a strong suspicion of atrial arrhythmia, for example in survivors of cryptogenic stroke (1). If the patient presents with rare episodes of symptomatic arrhythmia, diagnostics could be prolonged with an implantable loop recorder (66).

1.6.3 Photoplethysmography for AF screening

Photoplethysmography (PPG) can determine someone's pulse by measuring changes in the blood flow between systole and diastole in peripherical tissue (e.g., fingers or ears). This

technology is in daily clinical use since many years in the form of pulse oximetry. Because of advances in technology of consumer electronics, nowadays smartphones can adequately detect PPG signals via their camera. The high availability of smartphones in the population enables large self-screening campaigns without personal contact with medical personal (67). Due to algorithms based on artificial intelligence, it might soon be possible to even diagnose AF by analysis of PPG signals without ECG verification (68).

2 Introduction to subtopics

2.1 AF prediction

Since a significant proportion of patients with AF is asymptomatic or has only unspecific symptoms, identification of AF patients remains a cornerstone in stroke prevention in the general population. Even in populations where the probability for AF is high, it is not possible to identify every case of AF with ECG monitoring alone: In a study by Botto et al. (69), serial ECG Holter monitoring (i.e. four 24-hour Holter recordings or two seven-day Holter recordings per year) was associated with AF detection rates of 50-60% in a population with known AF. An approach to implant a loop recorder in every patient in whom AF is suspected remains infeasible due to cost and limited medical resources. Moreover, implanting loop recorders would be a very invasive method compared to other diagnostic tests that could potentially detect AF (e.g. an ECG recording or an AF prediction algorithm).

Magnani et al. analysed different methods for AF prediction (70). Rienstra et al. (71) gave a profound overview of the state-of-the-art in AF prediction. Both papers conclude that there is a high need for AF prediction, while large areas of uncertainty remain. Clinical parameters (such as CHA_2DS_2-VASc score) have been associated with the prevalence of AHRE and the precision can also be improved by biomarkers such as NT-proBNP (64). However, a considerable level of uncertainty remains (with AUC levels < 0.85) and missing validation from prospective cohorts impedes the use of developed scores in daily clinical practice.

2.1.1 ECG algorithms

The main goal of ECG algorithms is to identify ECG signs that are associated with the development with AF in the future. As automaticity of atrial tissue (especially in the pulmonary veins) is one of the main drivers of AF initiation (17), atrial extrasystoles with

P waves from sources other than the sinus node may be predictive of AF development. Consequently, the morphology of P waves and the incidence of supraventricular extrasystoles are have been included in contemporary AF prediction algorithms.

There are several groups working on AF prediction from surface ECGs, such as Stafford et al. (72), Perez et al. (73), Cabasson et al. (74), Vassilikos et al. (75), Salah et al. (76), Bonizzi et al. (65), Martinez et al. (77), Alexander et al. (78), or recently, Nakatani et al. (79). None of these algorithms are established in clinical routine, due to insufficient prediction and missing evidence from prospective studies. Furthermore, it is unclear if such algorithms could increase the sensitivity and specificity of clinical risk scores and biomarkers already in use.

2.1.1.1 AF initiation algorithm

In cooperation with our institution, AIT Austrian Institute of Technology is currently developing different techniques to increase the accuracy of AF prediction in daily clinical practice.

The “AF initiation algorithm”, is based on surface ECG data (80). It could predict the occurrence of paroxysmal AF within the next few hours with an accuracy of 84 % (80, 81) and was also able to identify patients that developed AF within the following 12 months.

2.2 AF and TAVI

2.2.1 Aortic stenosis (AS)

Aortic stenosis (AS) is defined as stenosis of the aortic valve (82), which represents the valve between the left ventricle and the aorta (Figure 6). With a prevalence of 12% in patients > 75 years, (83) AS is the most prevalent valvular heart disease in the developed world. It is a progressive disease that leads to a five-year survival between 38% and 83% if untreated (84).

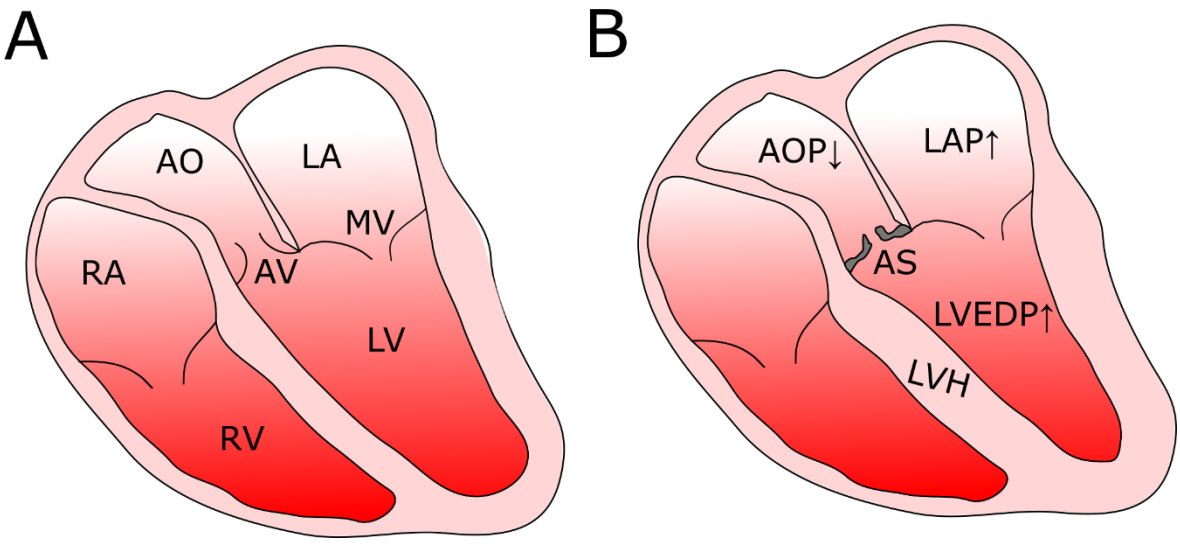


Figure 6. Schematic view of the apical 5-chamber view of the heart (A) and changes in AS (B). AS: aortic stenosis; AV: aortic valve; LA: left atrium; LV: left ventricle; MV: mitral valve; RA: right atrium; RV: right ventricle. Please see text for further abbreviations.

2.2.1.1 Aetiology

There are two common causes of AS in adulthood: *calcific AS*, and *rheumatic AS*.

The most common cause is the calcific degeneration of the aortic valve. Atherosclerosis-like plaque forms on the aortic valve, which later transforms to solid calcium deposits. The main risk factor is age. A special type of calcific AS develops in patients with a bicuspid aortic valve, which represents the most common congenital valvular heart disease (85). The presence of a bicuspid aortic valve is the main cause of pre-senile aortic stenosis (86).

Rheumatic AS is the result of a destruction process during rheumatic fever. It is often associated with mitral regurgitation or mitral stenosis, and AF due to these valvular defects have special implications (1). Due to advances in treatment of bacterial infections, this type of AS has become very rare in the developed countries, but it is still present in developing countries (85).

2.2.1.2 Pathophysiology and symptoms

When the aortic valve narrows, a pressure gradient needs to be overcome to pump the same amount of blood through the aortic root. This increases the afterload of the left ventricle, which reacts by myocardial hypertrophy. The human body compensates the increased pressure requirement for many years until symptoms occur (Figure 7). The sequalae of the disease are caused by (1) inability of the left ventricle to generate adequate blood pressure or blood flow in the general arterial system, (2) reduced coronary blood flow while oxygen demand is increased due to hypertrophy and (3) increased pressure in the left ventricle during inflow.

The first symptoms appear at times of high demand of blood flow (e.g., during exercise) or when the heart has to compensate for sudden changes in blood pressure (e.g., during standing up). Aortic pressure (Figure 6: AOP) and systemic blood pressure falls. In these situations, vertigo or syncope as sign of cerebral hypoperfusion is one of the main symptoms of AS. Further progression of AS may lead to kidney or multiorgan failure.

Adequate systolic blood pressure can be sustained in case of reduced blood flow by increasing vascular tone of the arterial system, but at the expense of reduced diastolic pressure and diastolic flow. Angina pectoris is one of the key symptoms, since the coronary circulation drops due to low diastolic pressure (87) and hypertrophy increases myocardial oxygen demand.

Once the left ventricle is not able to maintain the required flow, the pressure during left ventricular inflow (i.e., left ventricular end-diastolic pressure, LVEDP, Figure 6) increases leading to increased pressure in the left atrium (Figure 6: LAP) and the pulmonary vascular system. This mechanism is amplified by impaired relaxation and increased stiffness of the left ventricle due to hypertrophy and fibrosis. The consequence is shortness of breath and pulmonary oedema as sign of left-heart failure.

Once the symptoms develop, the prognosis of the untreated AS dramatically worsens to a median survival of only a few years (Figure 7).

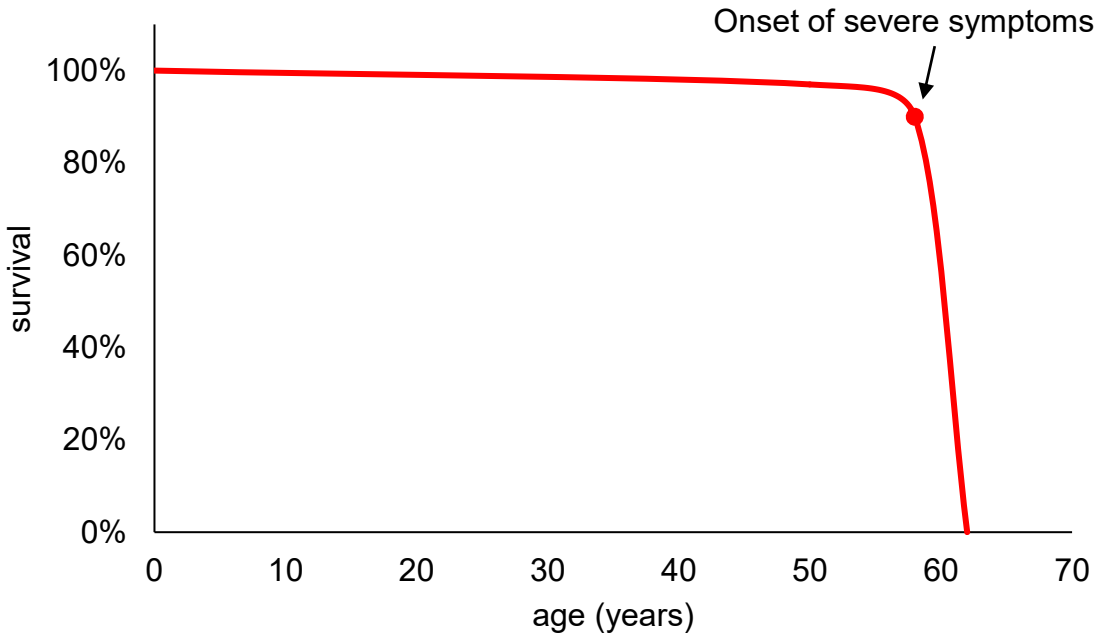


Figure 7. Natural progression of AS. After a long asymptomatic period with normal life span, survival declines dramatically after onset of symptoms. AS: aortic stenosis. Based on (85).

2.2.1.3 Assessment and classification

The gold standard for assessment of AS is echocardiography (82). The severity of AS is classified based on three different parameters: maximal velocity through the aortic valve, mean gradient during systole and aortic valve area (Table 4). Velocities and gradients can

be measured directly by doppler transthoracic echocardiography. The aortic valve area can be calculated using the continuity equation, which incorporates a number of measurements (i.e., aortic valve gradient, diameter and gradient of the left-ventricular outflow tract) and is therefore prone to error (88).

	max. velocity	mean gradient	valve area
mild AS	< 3 m/s	< 20 mmHg	> 1.5 cm²
moderate AS	3 – 4 m/s	20 – 40 mmHg	1.0 – 1.5 cm²
severe AS	≥ 4 m/s	≥ 40	≤ 1.0 cm²

Table 4. classification of AS, adapted from (82, 88).

In case of discrepancies between measurements, current guidelines propose a decision tree to guide through treatment indications. One subtype is low-flow low-gradient AS, defined as aortic valve area ≤ 1.0 cm² but mean gradient below 40 mmHg and maximum velocity below 4 m/s. This type of AS is common in patients with low cardiac output due to advanced heart failure.

2.2.2 Surgical aortic valve replacement

Until the early 2000's, surgical aortic valve replacement (SAVR) had been the only curative treatment option of AS (89). The procedure requires thoracotomy and extracorporeal membrane oxygenation to allow access of the aortic root. After explant of the diseased aortic valve, either a mechanical prosthesis or a bio-prosthesis is implanted. While SAVR has become a very safe procedure in patients with low or moderate operative risk, it still requires intensive post-operative care and a hospital stay of a week (90).

As calcific AS more frequently develops in the elderly, many AS patients have a high or prohibitive operative risk due to their age and comorbidities at the time of diagnosis. Until

the development of transcatheter aortic valve implantation (TAVI), physicians had only limited options for treatment.

2.2.3 Balloon valvuloplasty

As an ultima ratio, the aortic valve can be burst by a percutaneously introduced balloon. This procedure is catheter lab based, but the beneficial effect lasts only a few months. This treatment is an option for patients deemed unsuitable for both SAVR and TAVI or as a bridge to a definite therapy in emergency situations.

2.2.4 TAVI

TAVI has first been performed in 2002 (89) and it is now an established treatment alternative to SAVR for patients with severe AS. The aortic valve is normally accessed retrogradely via arterial puncture (Figure 8A). Predominantly, the femoral artery is used, but other access sites (such as trans-subclavian or trans-aortic) are feasible. If the vessel conditions do not permit arterial access, mini-thoracotomy and transapical puncture of the left ventricle may be used (Figure 8A). After introducing a wire through the aortic valve in most cases balloon valvuloplasty is performed. Afterwards, a valve prosthesis is introduced and expands at the site of the original valve (Figure 8B). This procedure requires mild sedative analgesia only (if no surgical access is required) and lasts approximately one hour. It may therefore be performed in patients with a high number of comorbidities and a high perioperative risk.

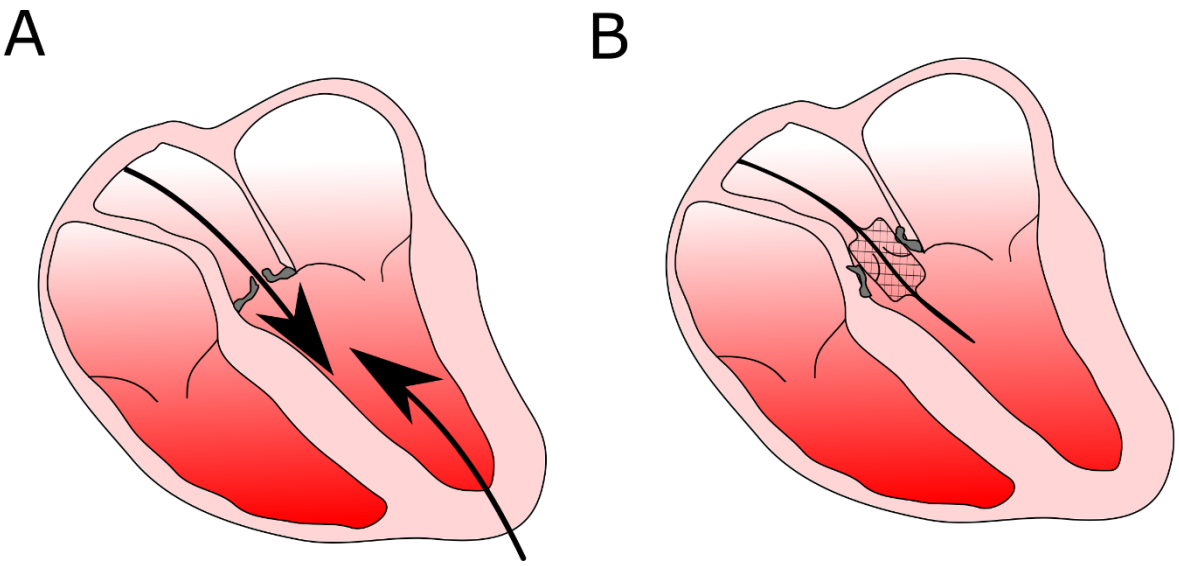


Figure 8. Schematic figure of different strategies of access for TAVI and the TAVI procedure itself. TAVI: transcatheter aortic valve implantation.

In 2014, Mack et al showed significantly higher survival of TAVI compared to SAVR in patients with high surgical risk (91). Since many AS patients fit this criteria, the number of TAVI's has skyrocketed in the last few years, outrunning the number of total SAVR procedures in Germany (92). Recent studies led to a Federal Drug Administration (FDA) approval even for low risk patients (90). According to current ESC guidelines, the decision whether to perform TAVI or SAVR should be chosen by an interdisciplinary heart team, with TAVI being favoured in patients with high surgical risk (82).

2.2.5 AF and AS

In patients with severe AS, coexisting AF has been shown to be more frequent (93) and an independent predictor for lower survival (94). However, the impact of pre-existing AF on a TAVI procedure is controversial (95).

2.2.6 NOAF

NOAF is the most common arrhythmia after SAVR (incidence 7-64%) (96-98) and has been associated with lower 1-year survival (99). However, concerning TAVI only limited data was available (96, 100).

2.3 AF and non-medicinal stroke prevention

2.3.1 LAAC

The percutaneous closure of the left atrial appendage (Figure 9) is a relatively new procedure and was first performed in 2002 (101). The rationale behind LAAC is the exclusion of the left atrial appendage, which appears to be a predilection site for cardiac thrombi in AF[2] in patients with risk of cardioembolic stroke. Several minimally invasive techniques have been developed to seal the left atrial appendage.

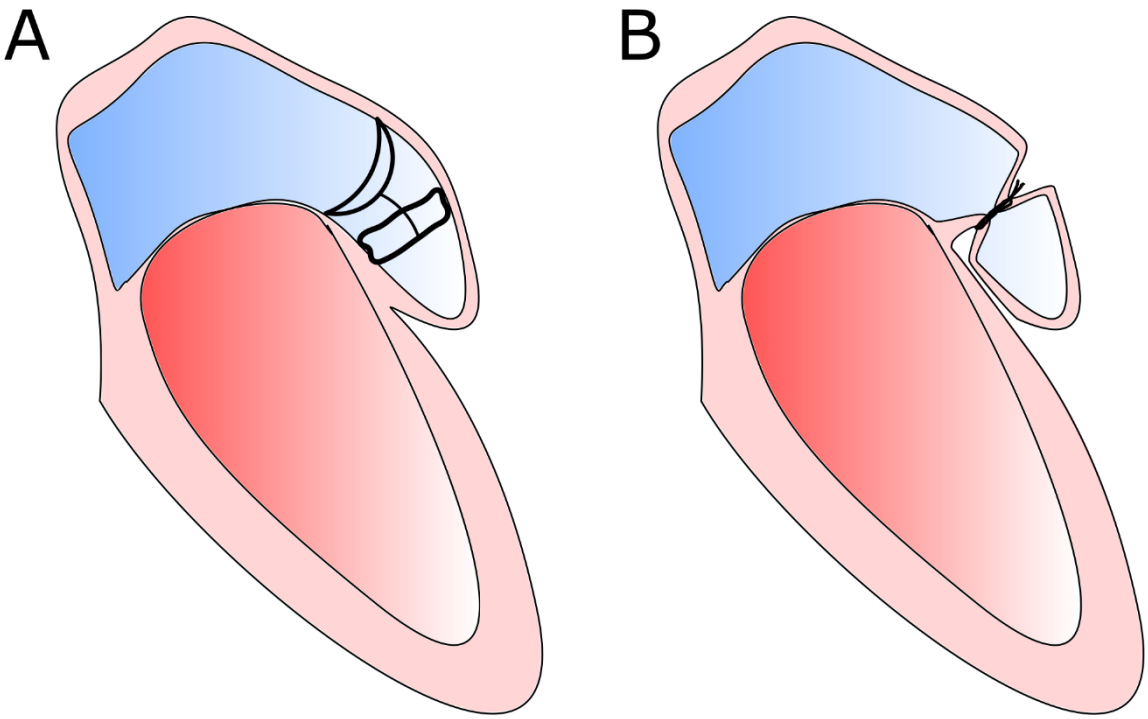


Figure 9. Principle of endocardial (A) and epicardial (B) LAAC devices. LAAC: left atrial appendage closure

2.3.1.1 Endocardial devices

Most LAAC devices use the *endocardial access* (Figure 10). After incision of the femoral vein, a catheter is inserted into the lower vena cava to the right ventricle. Under

[2] More information can be found in chapter 1.4.1.1 (page 10).

fluoroscopy, TOE or intracardial echocardiography (ICE) guidance, the interatrial septum is punctured to gain access to the left atrium. Finally, the device is implanted into the left atrial appendage (102).

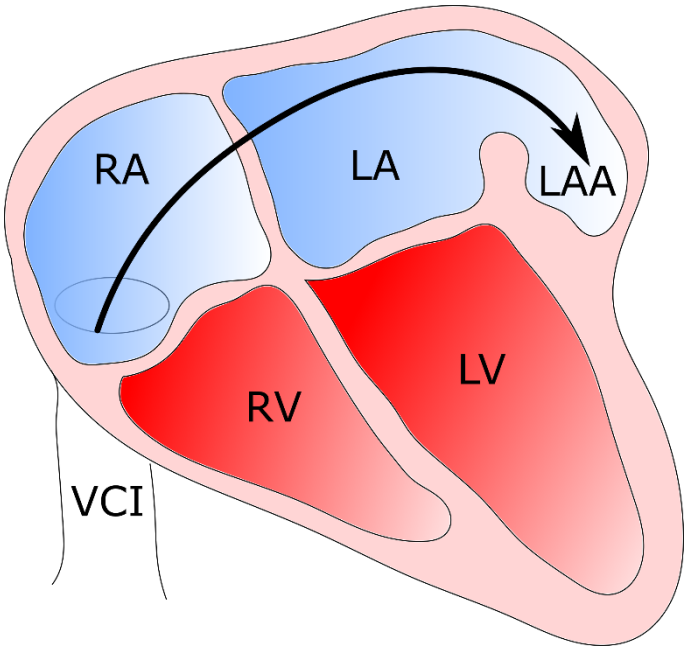


Figure 10. Endocardial access of the LAA by transseptal puncture. LA: left atrium; LAA: left atrial appendage; LV: left ventricle; RA: right atrium; RV: right ventricle; VCI: vena cava inferior.

Two tools are used to seal the left atrial appendage: *Plugs* obstruct the *neck* of the left atrial appendage with a *convex* surface, while *pacifiers* have an extra *concave* lobe that seals the *ostium* (Figure 9A). Current evidence does not favour one device over the other (23).

The following endocardial LAAC devices are currently commercially available and CE-mark approved (23):

- WATCHMAN, WATCHMAN FLX (Boston Scientific®, Marlborough, MA)
- WaveCrest (BiosenseWebster®, Johnson & Johnson, New Brunswick, NJ)
- AMPLATZER Cardiac Plug, AMPLATZER Amulet (Abbott Laboratories®, North Chicago, IL)

- Ultraseal LAA Occluder (Cardia®, Eagan, MN)

- LAmbre (Lifetech Scientific®, Shenzhen, China)

2.3.1.2 Epicardial devices

The advantage of the *epicardial access* (Figure 9B) is the avoidance of an endocardial device, therefore limiting the risk of bleeding, embolism or systemic infection at follow up (23). However, during implantation, both endovascular and epicardial accesses are needed (103). Under general anaesthesia and TOE guidance, the anterior epicardial space is accessed. Additionally, access to the left atrium is gained via transseptal puncture.

The only currently available device is the LARIAT (SentreHEART®, Palo Alto, CA)

2.3.1.3 Suitable patient populations

LAAC was initially thought to be "an alternative to OAC treatment for all patients with non-valvular AF" (104), with the possibility to avoid lifelong treatment with anticoagulants. However, OAC is currently considered safe and effective in most patients (1) and also feasible in patients with high bleeding risk (54). Every patient undergoing LAAC faces a certain risk of procedural complications while not everyone benefits from it. LAAC does not reduce stroke risk to zero and a significant proportion of patients may not suffer from stroke even without LAAC (23).

In patients who are eligible for OAC without elevated bleeding risk, the PROTECT AF and PREVAIL studies examined LAAC vs. warfarin, and came to diverging results (105, 106). For this indication, LAAC is generally FDA-approved, but the current EHRA / European Association of Percutaneous Cardiovascular Interventions (EAPCI) consensus statement suggests this procedure only in patients who are completely unwilling or unable to take OAC despite adequate education (107).

In patients with contra-indication to long-term OAC, such as a history of severe intracranial or gastrointestinal bleeding, LAAC is currently indicated according to ESC guidelines for the treatment of AF (class of recommendation IIb, level of evidence B) (1), as non-randomized registries suggest better outcome compared to no therapy (108, 109). However, discrepancies between the exact definition of *contra-indication to OAC* exist (1).

A borderline indication represents elevated bleeding risk under OAC. DOACs have been proven effective and safe in preventing stroke and therefore represent a valid alternative to VKA treatment (1). Only randomized controlled study comparing LAAC to DOACs has been published (110). In patients with elevated bleeding risk, the decision to perform LAAC warrants careful assessment of risk and benefits of LAAC vs. DOACs (23).

In patients with ischaemic stroke despite OAC therapy, LAAC is a viable option and it is also discussed in current ESC guidelines (1).

3 Studies

3.1 Research questions

Considering the existing evidence, several questions remain open in terms of the prediction of AF, AF in TAVI patients and non-medicinal stroke prevention. I developed and conducted three different investigations during the doctoral studies. They are described in the following section.

3.1.1 AF prediction

The aforementioned "AF initiation algorithm" had not yet been tested in a prospective study. Furthermore, the application was limited to patients without CIED. The SAFE-ME study was therefore created to prospectively test the algorithm, to broaden its applicability to patients with a CIED and to optimize its effectiveness by including other technical and clinical parameters.

3.1.2 AF and TAVI

There are only few studies available regarding the prevalence and effect of pre-existing and new-onset AF on TAVI patients and their results are conflicting. The rationale of the AF-TAVI study was therefore to explore 1) the one-year outcome of patients with pre-existing AF undergoing TAVI and 2) the incidence, predictors and outcome of NOAF after TAVI.

3.1.3 Austrian LAAC Registry

While about most patients undergoing LAAC have a history of severe bleeding as indication (108, 109), the remaining patient population is very heterogeneous. It ranges from young, healthy individuals, unwilling to take OAC, to old patients with a high number of comorbidities. As a result, outcome after LAAC may vary depending on co-existing diseases and the indication to perform LAAC. Until today, there is only limited

data available concerning the exact indication which led to the decision to perform LAAC and outcome. An analysis of the Austrian LAAC registry was therefore performed to investigate in the specific indications to perform LAAC and their influence on outcome.

3.2 SAFE-ME study

The aim of the *Prospective database for prediction of atrial fibrillation in pacemaker and ICD patients* (SAFE-ME study) was to gather prospective data from a large cohort of CIED patients to develop tools for the prediction of AF. The study focusses on the development of models for more accurate prediction of AF based on clinical, ECG and device data, including the AF initiation algorithm. Ideally all prognostic parameters would be incorporated into one model.

3.2.1 Methods

We planned to prospectively investigate 250 patients with implantable pacemaker/cardioverter-defibrillator and an atrial lead into this study. We collected clinical data, device data, biomarkers and performed a 24-hour Holter ECG. After 6 months, the occurrence of AHRE and adverse events was documented. The ethics committee of the Medical University of Graz approved the study (29-229 ex 16/17).

3.2.1.1 Study subjects

We selected patients with CIEDs device as study population, as this population's atrial rhythm is continuously monitored. CIEDs are capable of documenting atrial arrhythmias, even with a duration of only a few seconds. However, the atrial lead is necessary to exactly determine the atrial rate. Therefore, only patients with CIED and atrial lead were included into the study.

Most algorithms based on surface ECG data depend on the detection of premature supraventricular beats and on the analysis of the P wave morphology of such beats. Therefore, atrial stimulation of the CIED had to be largely excluded – at least for a certain portion of the Holter ECG (atrial stimulation rate ≤ 50 %), in order to provide sufficient

data. However, ventricular pacing is not expected to influence the algorithms performance. Since AF should be predicted from signals in sinus rhythm, patients with a high probability of showing AF during Holter ECG (mode switch rate > 50 % or AF during CIED interrogation) were excluded from the study.

For generalisability, we included patients of all risk groups, either AF-naïve or with previously documented episodes of AF. To ensure diagnostic value, patients with low stroke risk and therefore no clear indication for anticoagulation (defined as CHA_2DS_2-VASc score ≤ 1) were not included.

The study plan with definite inclusion and exclusion criteria is shown in Figure 11.

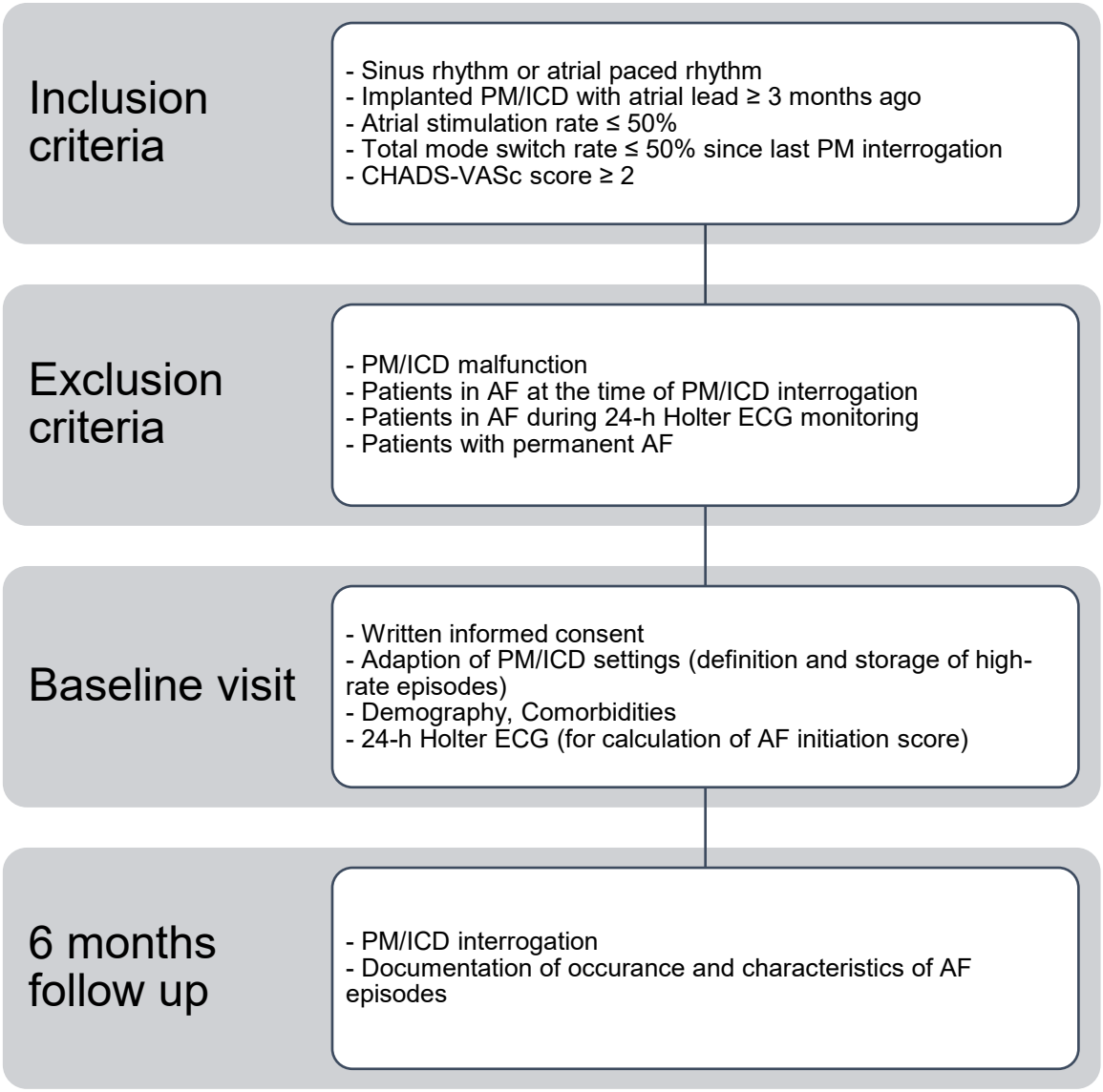


Figure 11. Study plan of the SAFE-ME study. AF: atrial fibrillation. ECG: electrocardiogram. ICD: implantable cardioverter-defibrillator, PM: pacemaker.

3.2.1.2 Baseline visit

After recruitment in our pacemaker outpatient clinic and after obtaining written informed consent, we gathered information on demographic details, comorbidities (including history of AF), medication and risk scores (CHA_2DS_2-VASc score, HAS-BLED score) of study patients. The case report form can be found in the appendix.

During this baseline CIED interrogation, automated ECG storage for high-rate episodes was enabled. To gather biomarkers for the development of AHREs, lab testing for C-reactive protein, nt-ProBNP and creatinine was performed. Blood samples were planned to be stored in the study centre's biobank for post-hoc biomarker analyses. Additionally, transthoracic echocardiography allowed the assessment of left ventricular dimensions, left ventricular function, and left atrial size.

After completion of the baseline visit, a 24-h Holter ECG with an ECG monitor was performed. The digitalized and pseudonymized ECG data was planned to be transferred to AIT for optimization of an ECG algorithms. However, AIT did not gain access to the patients' personal data.

3.2.1.3 Holter monitoring system

We used a 3-channel Holter ECG monitor "ECGpro Holter EP 820" (Amendtec®, Germany) for 24-hour ECG monitoring. After the monitoring period, the ECG data was transferred to the hospital's information system. For medical evaluation, data was analysed automatically by ECGpro Holter ECG management software. A physician of the study team performed a manual analysis and confirmed potential arrhythmic episodes. If there were any abnormalities requiring further diagnostic tests or treatment, the patient was contacted immediately.

After anonymization, ECG data and clinical data was transferred to AIT via a USB storage device or via encrypted telecommunication services (via Secure File Transfer Protocol).

3.2.1.4 Follow up

After 6 months, patients were reassessed during their regular CIED interrogation in at our outpatient clinics. Specifically, we interrogated the CIED for AHRE during the study

period (including intracardiac electrogram recordings), and monitored the time point of first occurrence, episode duration and total number and frequency of atrial high rate episodes.

3.2.1.5 AF initiation algorithm

The "AF initiation algorithm" currently under development by AIT uses Holter ECG data. Details have previously been published (80). The algorithm detects premature beats with supra-ventricular origin other than the sinus node. Supra-ventricular beats are identified by comparing the QRS morphology to the most recent morphology class, requiring 20% prematurity based on the first derivative of the sequence of the RR intervals.

A representative P-wave template $P_{average}$ is generated by coherent averaging of the respective signal part of all "normal" heart beats. Subsequently, all regular (i.e. not premature) and all premature P waves P_i are compared to this P wave template by calculating a correlation coefficient cc_i in between each P wave P_i and the template.

The two groups of correlation coefficients corresponding to the regular ($cc_{regular}$) and the premature heartbeats ($cc_{premature}$) represent two sets of samples.

If the conduction through the atria is varying for supraventricular premature beats – represented by varying P wave morphologies – the probability for AF is increased (111). Therefore, a non-parametric U-test is applied to the two groups of correlation coefficients in order to assess the probability $p_{u\text{-}test}$ that both samples stem from the same distribution, i.e. that premature and regular P waves exhibit equal morphologies. The negative decade logarithm of this value serves as the PAF screening parameter p_{init} or "AF initiation score".

After completion of the follow up, the incidence and characteristics of AF episodes were planned to be communicated to AIT to allow optimization of the ECG algorithm. Data

would be analysed to investigate the most influential parameters (e.g. P wave morphology or rate of premature beats). The "AF initiation score" would then be correlated with different characteristics of AF episodes (e.g. time to first incidence, maximum duration, total duration, frequency). Additionally, various parameters of the algorithm should be optimized and the impact of short episodes of atrial tachycardia on the development of AF would be evaluated.

The use of multivariable statistical models was planned, such as decision trees and random forests, for prediction of future AF. These models would consider both, the ECG based prediction score and other clinical data. SAFE-ME would give a first impression of the power of such techniques.

3.2.1.6 Time schedule

This project was launched in March 2017. We planned to recruit patients until January, 2018, but due to a slow inclusion rate, we prolonged the inclusion period to the end of 2020 (Figure 12).

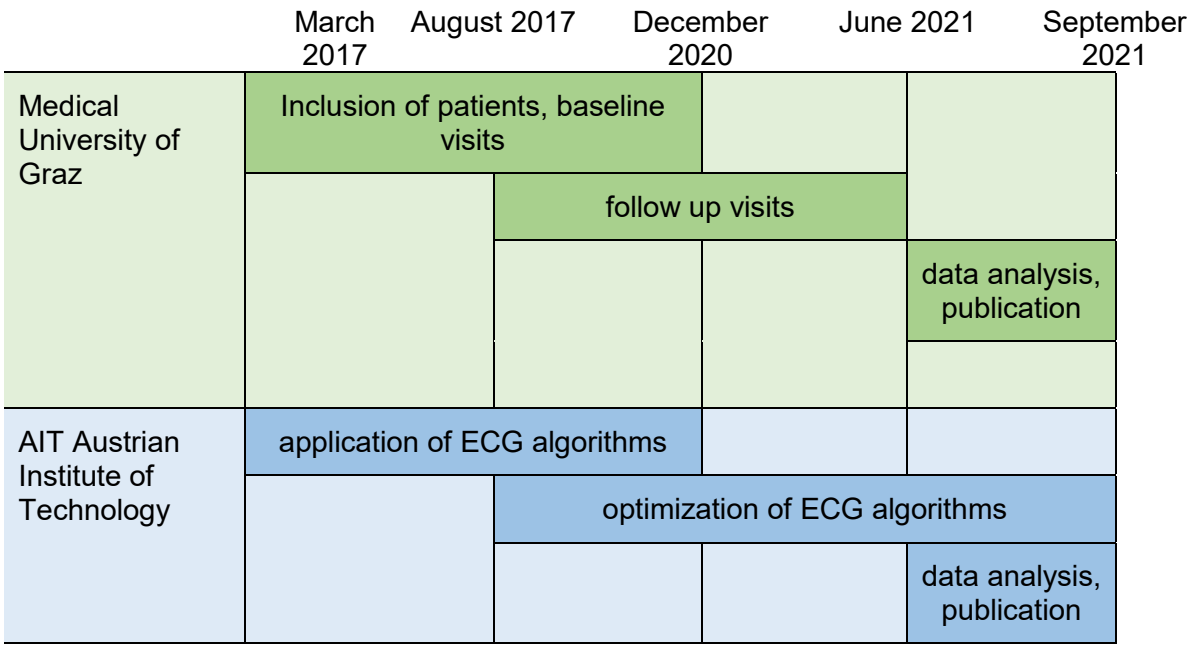


Figure 12. Anticipated timeline of the SAFE-ME study.

3.2.1.7 Statistics

Results are given as mean (standard deviation), median (interquartile range) or number (proportion), where appropriate. In this analysis, patients that developed AHRE at follow up were summarized as "AHRE group" and compared to remaining patients without AHRE but complete follow-up ("No-AHRE group") in bivariable analysis, using Mann-Whitney-U test and Fisher's exact test.

Additionally, the comparison of the ECG algorithm's result with the incidence of AHRE episodes was planned by ROC curve. Another goal was to establish a combined AF prediction score that includes both clinical factors, device data and the result from the ECG algorithm.

As the study was designed as pilot study, we estimated that a sample size of 100 was representative for the current study (112).

All statistical analysis was performed with the software package SPSS for Windows (IBM, IL, USA).

3.2.2 Results

3.2.2.1 Enrolment rate and study adaptations

The study progression was monitored and adaptations to the original study were discussed by the investigators at regular intervals. In the early phases of the study, we noted that the progress was slower than expected. To keep up with the timeline, we made the following changes to the original protocol:

- Support by a medical student
- Complete suspension of blood sample storage in the biobank

- Continuation of lab testing as optional procedure
- Continuation of echocardiography as optional procedure

The recruitment period was stepwise prolonged (currently until December 2020).

3.2.2.2 Included patients

By April 2020, 42 participants were recruited. One patient had to be excluded because inclusion criteria were not fulfilled (atrial stimulation rate > 50%) and two patients had AF during the Holter analysis (Figure 13). In one of these patients, AF was already known. The other patient was contacted prematurely to initiate OAC because of newly-diagnosed AF. In total, we included, 39 patients into the per protocol analysis.

3.2.2.3 Baseline characteristics

Mean age was 76±7 years and 38.5% were female. Median CHA_2DS_2-VASc score was 4 (IQR 3-4) and median HAS-BLED score was 1 (IQR 1-2). Most prevalent comorbidities were arterial hypertension (76.9%), coronary artery disease (36.1%) and diabetes mellitus (30.8%). Paroxysmal atrial fibrillation was prevalent in 10.3% of patients. More than three quarters took antihypertensives and 25.6% had OAC at baseline. Other baseline characteristics are listed in Table 5.

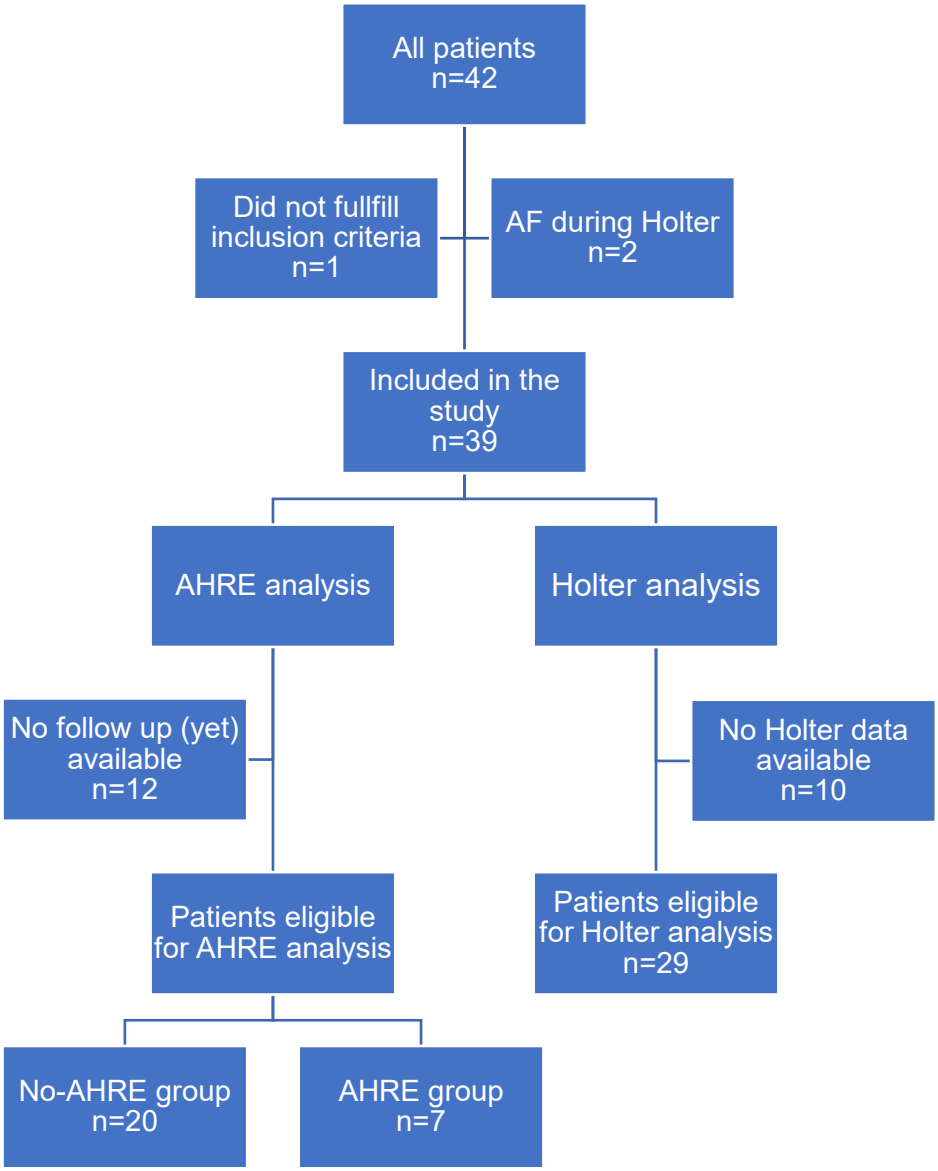


Figure 13. Flow chart of this interim analysis of the SAFE-ME study.

Table 5. Baseline characteristics of all included patients, AHRE group and no-AHRE group. AF: atrial fibrillation; AHRE: atrial high rate episode.

parameter	all patients	AHRE group	No-AHRE group	P value
count	39	7	20	N/A
female gender	38.5%	42.9%	25.0%	0.633
age (years)	76±7	76±7	76±6	0.935
body mass index (kg m^{-2})	26.7±4.7	25±3	27±5	0.198
body surface area (m^2)	1.86±0.20	1.81±0.14	1.89±0.18	0.263
systolic blood pressure (mmHg)	154±24	157±22	155±24	0.919
diastolic blood pressure	85±14	91±12	86±14	0.609
comorbidities				
arterial hypertension	76.9%	85.7%	90.0%	1.000
coronary artery disease	36.1%	50.0%	38.9%	0.665
diabetes mellitus	30.8%	57.1%	15.0%	0.0496
vascular disease	17.9%	14.3%	25.0%	0.656
history of percutaneous intervention	17.9%	28.6%	15.0%	0.580

parameter	all patients	AHRE group	No-AHRE group	P value
previous stroke, transitory ischemic attack or thromboembolism	15.4%	42.9%	15.0%	0.290
previous cardiac surgery	15.4%	14.3%	15.0%	1.000
abnormal renal function	10.3%	14.3%	10.0%	1.000
history of AF	10.3%	28.6%	10.0%	0.269
congestive heart failure	10.3%	0%	10.0%	0.601
previous thrombosis	7.7%	14.3%	5.0%	0.459
periphery artery disease	7.7%	0%	10.0%	1.000
previous stroke	5.1%	14.3%	5.0%	0.459
abnormal liver function	2.6%	0%	5.0%	1.000
risk scores				
CHA_2DS_2-VASc score	4 (3-4)	4 (4-5)	4 (3-4)	0.072
$CHADS_2$ score	1.9±1.0	2.7±0.8	2.0±1.0	0.081
HAS-BLED score	1 (1-2)	2 (1-2)	1 (1-2)	0.145
medication				
antihypertensives beta blockers	76.9% 43.6%	71.4% 57.1%	90.0% 35.0%	0.269 0.391

parameter	all patients	AHRE group	No-AHRE group	P value
aspirin or P_2Y_{12} inhibitor	41.0%	28.6%	35.0%	1.000
statins	35.9%	42.9%	30.0%	0.653
OAC DOAC VKA	25.6% 15.4% 10.3%	67.1% 28.6% 28.6%	15.0% 10.0% 5.0%	0.077
metformin	15.4%	14.3%	10.0%	1.000

3.2.2.4 Device details

Most patients (94.8%) had a dual chamber pacemaker (Table 6). One patient previously had received a pacemaker suitable for cardiac resynchronization therapy. No patient with ICD was included. The last device change had been performed 16 (5-51) months ago and the last lead implantation or revision before 49 (15-99) months. The most prevalent indication was AV block (82.1%). Mean atrial stimulation rate was 19% and median ventricular stimulation rate was 86%. Since the last reset of the CIED storage (which had been performed 11 [3-12] months ago), AHRE's were documented in 35.9%, which led to a mode switch rate of ≥ 1% in 12.8%. Episodes of non-sustained ventricular tachycardia occurred in 12.8% of patients.

parameter	all patients	AHRE group	No-AHRE group	P value
device type				0.259
dual-chamber pacemaker	94.8%	85.7%	100%	
CRT	2.6%	0%	0%	
AAI pacemaker	2.6%	14.3%	0%	
indication				1.000
AV block	82.1%	85.7%	85.0%	
sick sinus syndrome	12.8%	14.3%	10.0%	
carotid sinus syndrome	2.6%	0%	5.0%	
dilatative cardiomyopathy	2.6%	0%	0%	
device manufacturer				0.243
Medtronic®	46.2%	48.1%	57.1%	
Biotronik®	23.1%	22.2%	14.3%	

LivaNova® Abbott® Boston Scientific®	12.8% 12.8% 5.1%	18.5% 14.3% 3.7%	0% 5.0% 14.3%	
R sensor activated	35.9%	57.1%	30.0%	0.365
atrial stimulation rate (%)	19±15	22±18	19±16	0.725
ventricular stimulation rate (%)	86 (0-100)	71 (0-100)	84 (0-100)	0.778
time since last AHRE reset (months)	11 (3-12)	6 (3-11)	11 (3-12)	0.766
previous occurrence of AHRE	35.9%	71.4%	20.0%	0.023
mode switch rate ≥ 1%	12.8%	28.6%	0%	0.060
previous nsVT	12.8%	14.3%	10.0%	1.000

Table 6. Device details of included patients. AV: atrioventricular; CRT: cardiac resynchronization therapy; AHRE: atrial high rate episode; nsVT: non-sustained ventricular tachycardia.

3.2.2.5 Echocardiography and laboratory parameters

Echocardiography data is available for 51.3% of patients. Mean left ventricular end-diastolic diameter was 47±6 mm. Left ventricular function was normal (ejection fraction >50%) in 73.7%, moderately reduced in 15.8% and severely reduced (< 35%) in 10.5%. Mean E/E' was 12.8±6.9. The size of the left atrium was 39±6mm (short axis) and 49±7 mm (four chamber view). Mean right atrial size (four chamber view) was 46±6 mm.

Blood testing was performed in 48.7% of patients. Median nt-proBNP was 285 (165-676) pg/mL, C-reactive protein was 2.4 (1.4-4.2) mg/L and creatinine was 1.0 (0.8-1.2) mg/dL.

3.2.2.6 Holter analysis

All included patients received 24-hour Holter ECG monitoring immediately after the inclusion. During medical analysis of Holter ECG data, no pathologies requiring intervention were observed.

Due to technical problem, raw Holter ECG data of 10 patients (25.6%) was deleted by the Holter ECG system prematurely and was therefore not available for further analysis by AIT, reducing the number of eligible patients for Holter analysis to 29 (Figure 13). Since there was too little data, we could not calculate the "AF initiation score" and perform associated analyses. Holter ECG data will be sent to AIT for further analysis once the number of eligible patients rises to 50.

3.2.2.7 Follow up

Follow-up data is available for 69.2% of patients, which corresponds to all patients with an inclusion > 6 months before this analysis. Patients with available follow up were comprised into the "AHRE analysis group" (Figure 13). Follow-up visits were performed 190±13 days after inclusion.

3.2.2.8 Adverse events

During follow-up, three patients (11.1%) were hospitalized due to non-cardiovascular reasons (preparation for dialysis, investigation for prostatic hyperplasia, and femoral neck fracture). Mortality at follow-up was 0%.

3.2.2.9 Device checks and AHRE episodes

During follow-up device checks, no pathologies requiring intervention were found. No patient was in AF at follow-up and 40.7% were paced. Median atrial stimulation rate was 10 (2-21) % and ventricular stimulation rate was 2 (0-99) %.

AHRE occurred in seven patients (25.9%, “AHRE group”), with two patients (7.4%) having a mode switch rate ≥ 1%. The median number of AHRE episodes was 10 (IQR 1-6065). The longest episode lasted more than 15 seconds in 57.1% and more than 5 minutes in 42.9%. None of the patients reported symptoms during the arrhythmia episodes (corresponding to an AHRE symptom score of 1).

3.2.2.10 Predictors of AHRE episodes

In bivariable analysis, previous AHRE episodes (p=0.023) and diabetes mellitus (p=0.0496) were significantly associated with the occurrence of AHRE episodes at follow up.

3.2.2.11 AF prediction algorithm

Since the sample size needed for the AF prediction algorithm to produce accurate results was not yet attained, we did not apply the AF prediction algorithm onto the data of this interim analysis.

3.3 AF-TAVI study

3.3.1 Methods

To analyse the incidence of NOAF and effect of pre-existing AF and NOAF on outcome after TAVI, we performed a monocentric, retrospective analysis. The study was approved by the ethics committee of the Medical University of Graz (27-114 ex 14/15) and has been published in the Journal of Electrocardiology in 2017 (113).

3.3.1.1 Procedure

All patients undergoing TAVI between May 2007 and May 2014 at the Department of Cardiology, University Hospital of Graz, Austria, were included in the study. All periprocedural and postprocedural complications were recorded and defined according to recommendations of the Valve Aortic Research Consortium-2 criteria (114).

3.3.1.2 Post-procedural monitoring

Patients were monitored with continuous telemetry up to 48 hours after discharge from intensive care unit (ICU). Afterwards, daily ECG's were recorded. If symptoms of arrhythmia occurred, additional ECG recordings were performed.

3.3.1.3 Follow up

Patients were seen in the outpatient clinic at 3, 6 and 12 months for follow-up examinations, including echocardiography and 12-lead electrocardiogram recordings.

3.3.1.4 Data collection

Signed informed consent for the procedure and post-procedural follow up was provided by all patients. For this report, patients' files of our hospital's electronic and physical archives were reviewed for baseline characteristics, procedural and post-procedural outcome. To

ensure complete follow-up regarding rehospitalizations, files of all regional hospitals were accessed. If outcome data was missing, we obtained the information via telephone calls.

3.3.1.5 Statistical analysis

Data are expressed as mean ± standard deviation, median (interquartile range) or count (percentage), if appropriate. For paired sample analysis, the Wilcoxon singed rank test was used, while the Mann-Whitney-U-Test and Fisher's exact test were used for unpaired samples. For multivariable analysis, all univariable predictors with a p-value under 0.1 were considered as possible confounders. Additionally, the presence of interatrial block (IAB) (100) in baseline ECGs of NOAF patients was compared with those of a matched control group of no NOAF patients in a post-hoc analysis. Missing values were replaced by mean or median, where appropriate. A two-sided significance level of 0.05 was applied for all calculations.

The "R" statistical package (The R Foundation for Statistical Computing, Vienna, Austria) with "matchit" library and "nearest" method was used to match for gender and age. All other analyses were performed with IBM® SPSS® Statistics 20 (IBM Corporation, Armonk, NY).

3.3.2 Results

3.3.2.1 Baseline characteristics

A total of 398 consecutive patients undergoing TAVI were included into the analysis. Baseline characteristics are shown in Table 7. Patients with a median age of 82 (78-85) years were included, of which 63% were female. Median predicted 30-day mortality was 5.9% based on EuroSCORE II (115) and 6.4% based on German AV Score (94). In terms of comorbidities, patients suffered mostly from arterial hypertension (83%), coronary

artery disease (71%) and peripheral or central artery disease (41%). Pre-existing AF was prevalent in 172 patients (43%). Symptomatic heart failure, corresponding to NYHA III-IV, was prevalent in 75% of patients. Thirty-six per cent of patients were anticoagulated, 61% were on antiplatelets. Beta blockers were the most common antiarrhythmic drugs (60%), followed by digoxin (15%) and class III antiarrhythmics (2%). Ten percent of patients had an implanted pacemaker.

Patients with pre-existing AF had a higher prevalence of diabetes mellitus type 2, previous valve surgery, elevated troponin T levels and reduced left ventricular function (assessed by echocardiography, Table 7) compared to other patients. Consequently, risk scores shoed a significantly higher risk of mortality in those patients ($p<0.01$ for all). As expected, anticoagulants, beta blockers and digoxin were used significantly more frequently in the pre-existing AF group ($p<0.01$ for all).

Table 7. Baseline characteristics of treated patients.

	all patients	**pre-existing AF**	**NOAF**	**no NOAF**	**p^1**	**p^2**
epidemiology						
count	398	172	210	16	N/A	N/A
age, years	82 (78-85)	82 (78-85)	84 (79-87)	82 (78-86)	0.72	0.52
body mass index, kg m^{-2}	25 (23-28)	25 (22-28)	25 (21-27)	25 (23-28)	0.94	0.60
female gender	249 (63%)	65 (62%)	9 (56%)	133 (63%)	0.92	0.60
comorbidities						
arterial hypertension	330 (83%)	143 (83%)	14 (88%)	173 (82%)	1.00	1.00
coronary artery disease	283 (71%)	124 (72%)	9 (56%)	150 (71%)	0.74	0.26

	all patients	pre-existing AF	NOAF	no NOAF	p^1	p^2
extracardiac arteriopathy	161 (40%)	76 (44%)	5 (31%)	80 (38%)	0.22	0.79
cerebral arteriopathy	106 (27%)	49 (29%)	5 (31%)	52 (25%)	0.49	0.56
peripheral arteriopathy	81 (20%)	38 (22%)	1 (6%)	42 (20%)	0.45	0.32
previous percutaneous intervention	137 (34%)	60 (35%)	4 (25%)	73 (35%)	0.92	0.59
diabetes mellitus type II	117 (29%)	60 (35%)	2 (12%)	55 (26%)	0.04*	0.37
previous cardiac surgery	73 (18%)	32 (19%)	3 (19%)	38 (18%)	1.00	1.00
coronary arterial bypass surgery	60 (15%)	22 (13%)	3 (19%)	35 (17%)	0.26	0.74
previous valve surgery	20 (5%)	13 (8%)	2 (13%)	5 (2%)	<0.05*	0.08
cardiomyopathy	69 (18%)	36 (21%)	3 (19%)	30 (14%)	0.09	0.71
concentric LV hypertrophy	22 (6%)	11 (6%)	1 (6%)	10 (5%)	0.52	0.56
cardiomyopathy with reduced LVEF	47 (12%)	25 (15%)	0	20 (10%)	0.16	0.66
chronic obstructive pulmonary disease	63 (16%)	25 (15%)	1 (6%)	21 (10%)	0.16	0.72

	all patients	pre-existing AF	NOAF	no NOAF	p^1	p^2
neurological disease	56 (14%)	22 (13%)	1 (6%)	33 (16%)	0.56	0.48
porcelain aorta	54 (14%)	21 (12%)	1 (6%)	32 (15%)	0.45	0.48
dialysis	6 (2%)	1 (1%)	1 (6%)	4 (2%)	0.16	0.31
risk scores						
logistic EuroSCORE, %	13.3 (7.8-23.8)	15.3 (9.3-24.7)	12.2 (8.1-25.6)	11.2 (7.3-22.6)	<0.01*	0.61
EuroSCORE II, %	5.9 (3.2-10.8)	7.2 (4.4-12.8)	7.3 (3.0-9.6)	4.5 (2.8-9.6)	<0.01*	0.36
German AV Score, %	6.4 (3.8-10.3)	6.8 (4.7-12.7)	5.0 (4.1-8.1)	5.7 (3.3-8.0)	<0.01*	0.64
STS Score, %	6.3 (3.8-9.6)	6.6 (4.5-11.0)	5.1 (3.9-13.5)	6.0 (4.0-8.8)	<0.01*	0.90
CHA_2DS_2-VASc score	5 (5-6)	5 (5-6)	5 (4-6)	5 (5-6)	0.70	0.16
medication						

	all patients	pre-existing AF	NOAF	no NOAF	p^1	p^2
antiplatelets	241 (61%)	69 (40%)	13 (81%)	159 (76%)	<0.01*	0.77
anticoagulation	143 (36%)	120 (70%)	2 (13%)	21 (10%)	<0.01*	0.67
antiarrhythmics	246 (62%)	124 (72)	9 (56%)	113 (54%)	<0.01*	0.32
class II (beta blockers)	238 (60%)	121 (70)	8 (50%)	109 (52%)	<0.01*	1.00
digoxin	59 (15%)	52 (30)	0	7 (3%)	<0.01*	1.00
class III	7 (2%)	2 (1%)	1 (6%)	4 (2%)	0.70	0.31
class I	2 (0.5%)	1 (0.6%)	0	1 (0.5%)	1.00	1.00
others	5 (1%)	4 (2%)	0	1 (0.5%)	0.17	1.00
blood						
creatinine, µmol L^{-1}	98 (80-123)	106 (89-133)	91 (81-127)	90 (76-112)	<0.01*	0.59
elevated troponin T†	246 (62%)	96 (64%)	6 (67%)	82 (44%)	<0.01*	0.30
haemoglobin, g dL^{-1}	12 (11-13)	12 (11-13)	11 (10-13)	12 (11-13)	0.23	0.06

	all patients	pre-existing AF	NOAF	no NOAF	p^1	p^2
estimated glomerular filtration rate, ml min^{-1}	53 (39-66)	47 (36-61)	52 (35-76)	56 (43-72)	<0.01*	0.61
adjusted NT-proBNP, pg ml^{-1}	1443 (578-2930)	3297 (1678-5770)	1558 (363-3470)	1603 (625-4302)	<0.01*	0.80
albumin, g dL^{-1} (n=290)	4.1 (3.8-4.4)	4.1 (3.7-4.4)	4.2 (3.9-4.3)	4.2 (3.9-4.4)	0.07	0.95
cardiac devices						
implanted pacemaker	40 (10%)	28 (16%)	0	12 (6%)	<0.01*	1.00
haemodynamics						
systolic pulmonary pressure, mmHg	45 (33-60)	53 (41-65)	42 (29-56)	38 (30-50)	<0.01*	0.79
mean pulmonary pressure, mmHg	29 (21-37)	34 (26-41)	28 (19-36)	25 (19-33)	<0.01*	0.57
pulmonary capillary wedge pressure, mmHg	18 (12-24)	21 (26-41)	19 (10-23)	15 (10-20)	<0.01*	0.37
left ventricular end-diastolic pressure, mmHg	18 (13-23)	17 (13-21)	20 (15-28)	19 (13-24)	0.02*	0.35

	all patients	pre-existing AF	NOAF	no NOAF	p^1	p^2
aortic valve peak gradient, mmHg	52 (36-72)	47 (31-64)	62 (44-81)	57 (40-78)	<0.01*	0.62
aortic valve mean gradient, mmHg	45 (32-60)	41 (28-52)	56 (42-65)	48 (34-62)	<0.01*	0.44
indexed aortic valve area, $cm^2/1.72m^2$ (n=296)	0.53 (0.41-0.66)	0.53 (0.40-0.69)	0.46 (0.32-0.67)	0.54 (0.41-0.66)	0.71	0.27
echocardiography						
indexed left atrial 2D diameter, mm	57 (52-64)	61 (56-68)	56 (52-61)	54 (51-60)	<0.01*	0.34
indexed right atrial 2D diameter, mm	54 (49-60)	60 (53-67)	51 (49-58)	52 (47-55)	<0.01*	0.54
left ventricular end-diastolic diameter, mm	49 (43-54)	48 (43-53)	53 (46-55)	49 (43-54)	0.87	0.64
left ventricular function					<0.01*	0.42
> 50%	189 (62%)	67 (52%)	10 (71%)	112 (70%)		
31-50%	41 (14%)	22 (17%)	0	19 (12%)		

	all patients	pre-existing AF	NOAF	no NOAF	p[1]	p[2]
20-30%	54 (18%)	24 (19%)	4 (29%)	26 (16%)		
≤ 20%	19 (6%)	16 (12%)	0	3 (2%)		

EuroSCORE: European System for Cardiac Operative Risk Evaluation; STS: Society of Thoracic Surgeons; CRT: cardiac resynchronization therapy; ICD: implantable cardioverter defibrillator; BBB: bundle branch block. nt-ProBNP was adjusted for kidney function. †troponin T or high-sensitivity troponin T above 95% upper reference limit. [1] pre-existing AF vs others; [2] NOAF vs no NOAF patients. Reproduced from Zweiker et al. (113) with permission of publisher Elsevier (see Disclosures section for details).

3.3.2.2 TAVI Procedures

A self-expandable valve (Medtronic CoreValve, Medtronic, Minneapolis, MN) was used for all patients, via transfemoral (94%), trans-aortic (6%) and trans-subclavian (1%) approaches. Implantation, according to VARC-2 (114), was successful in 91% of cases.

Other patients either experienced improper valve function after implantation (n=21), implantation issues (i.e. rescue, malposition or valve-in-valve; n=19) or periprocedural death (n=3). Patients required catecholamines in 8 % and electrical cardioversion or defibrillation for ventricular arrhythmias in 3%. Immediate conversion to cardiac surgery including extra-corporal circulatory support was necessary in four patients (1%).

3.3.2.3 Rhythm disturbances before discharge

Out of 226 patients with previous SR after TAVI, 16 patients (7%) developed NOAF before discharge after TAVI. NOAF was first detected at a median of 1.5 days after procedure (interquartile range 1-2 days). Additionally, 23% of patients encountered a new left bundle branch block, and 15% received a permanent pacemaker.

3.3.2.4 In hospital outcome

Intrahospital complication rates were 34%, 44%, and 30% in the pre-existing AF, NOAF and no NOAF groups with no significant differences between groups (Table 8). The most common complication was pacemaker implantation (17% vs. 25% vs. 13%, p=ns). Acute kidney failure occurred only in the pre-existing AF group (n=7, $p<0.01$). Other complications were similar between all groups. In-hospital survival was 96%, 100% and 95% in no pre-existing AF, NOAF, and no NOAF groups (p=ns). ICU stay was insignificantly prolonged in the NOAF group vs. no NOAF group (median 2 [2-6] vs. 2 [1-

2] days, p=0.07). Total in-hospital stay was significantly longer in the pre-existing AF group compared to previous SR group (median 10 [8-14] vs. 8 [7-10] days, p<0.01).

Table 8. Intrahospital complications, length of stay and time-dependent mortality of treated patients.

	pre-existing AF	NOAF	no NOAF	p^1	p^2
any complication	58 (34%)	7 (44%)	62 (30%)	0.52	0.26
pacemaker implantation	29 (17%)	4 (25%)	28 (13%)	0.49	0.25
death	9 (5%)	1 (6%)	12 (6%)	1.00	1.00
cardiovascular death	7 (4%)	0 (0%)	10 (5%)	1.00	1.00
major bleeding	5 (3%)	0 (0%)	10 (5%)	0.60	1.00
minor bleeding	4 (2%)	1 (6%)	5 (2%)	1.00	0.36
life-threatening bleeding	5 (3%)	1 (6%)	2 (1%)	0.30	0.20
minor vascular complications	3 (2%)	0 (0%)	5 (2%)	1.00	1.00
cardiac tamponade	3 (2%)	1 (6%)	4 (2%)	1.00	0.31
stroke	2 (1%)	0 (0%)	5 (2%)	0.70	1.00
conversion to open surgery	1 (1%)	1 (6%)	5 (2%)	0.15	0.36
acute kidney injury	7 (4%)	0 (0%)	0 (0%)	<0.01*	1.00
cardiopulmonary bypass	1 (1%)	1 (6%)	2 (1%)	0.64	0.20
dialysis	4 (2%)	0 (0%)	0 (0%)	0.03*	1.00
pneumonia	2 (1%)	0 (0%)	1 (0%)	0.58	1.00
multi organ failure	0 (0%)	0 (0%)	2 (1%)	0.51	1.00

myocardial infarction	1 (1%)	0 (0%)	1 (0%)	1.00	1.00
severe aortic regurgitation	0 (0%)	0 (0%)	1 (0%)	1.00	1.00
length of stay					
ICU stay, days	2 (1-2)	2 (2-6)	2 (1-2)	0.86	0.07
total hospital stay, days	10 (8-14)	9 (7-14)	8 (7-10)	<0.01*	0.46
time-dependent mortality					
30-day mortality	12 (7%)	0	11 (5%)	0.39	1.00
1-year mortality	34 (20%)	1 (6%)	25 (12%)	0.02*	0.70

**: p<0.05. ICU: intensive care unit. [1] pre-existing AF vs others; [2] NOAF vs no NOAF patients. Reproduced from Zweiker et al. (113) with permission of publisher Elsevier (see Disclosures section for details).*

3.3.2.5 Follow up

We recorded out-of-hospital events until 1 year after procedure (Table 9), with the most common being rehospitalization. All-cause death and cardiovascular death were significantly more common in the pre-existing AF group compared to remaining patients (19.8% vs 11.5%, $p<0.01$ for overall death). There were no differences in mortality between no NOAF and NOAF groups (11.9% vs 6.3%, p=ns).

Rehospitalization occurred significantly more frequently in the NOAF group vs. the no-NOAF group (63% vs. 35%, p=0.03). Seven NOAF patients (44%) remained in AF during follow up visits, the other NOAF patients converted to SR within 3 months (n=7, 44%) or 6-12 months (n=2, 13%). During the first year of follow-up, four additional patients (2% of the no-NOAF group) developed AF within one year of follow up.

Any of the following events occurred once and only in the no NOAF group: major bleeding, minor bleeding, severe aortic regurgitation, transitory ischemic attack, pneumonia and multi organ failure.

Table 9. Out-of-hospital outcome and composite endpoints.

	pre-existing AF	**NOAF**	**no NOAF**	**p[1]**	**p[2]**
out-of-hospital complications					
any rehospitalization	81 (47)	10 (63)	73 (35)	0.04*	0.03*
cardiac rehospitalization	36 (21)	5 (31)	28 (13)	0.11	0.07
death	24 (14)	0	13 (6)	<0.01*	0.61
cardiovascular death	14 (8)	0	4 (2)	<0.01*	1.00
pacemaker implantation	30 (17)	4 (25)	34 (16)	0.79	0.31
acute myocardial infarction	3 (2)	0	3 (1)	1.00	1.00
stroke	3 (2)	1 (6)	0	0.32	0.07
acute kidney injury	2 (1)	0	1 (0.5)	0.58	1.00
endocarditis	0	0	2 (0.9)	0.51	1.00
composite endpoints according to VARC-2					
early safety (at 30 days)	151 (88)	15 (94)	191 (91)	0.32	1.00
clinical efficacy (at 365 days)	135 (78)	11 (69)	182 (87)	0.08	0.07
time-related valve safety (at 365 days)	147 (85)	12 (75)	178 (85)	0.78	0.29

[1] pre-existing AF vs others; [2] NOAF vs no NOAF patients. Reproduced from Zweiker et al. (113) with permission of publisher Elsevier (see Disclosures section for details).

3.3.2.6 Predictors of NOAF

In bivariable analysis, we found previous valve surgery and low haemoglobin levels to be associated with the development of NOAF (Table 10). In multivariable analysis, the only significant predictor was history of valve surgery (HR 5.86 [CI 1.04-32.94], $p<0.05$).

3.3.2.7 Predictors of long-term mortality

In bivariable analysis, pre-existing AF, dialysis, cardiomyopathy, peripheral artery disease, low albumin, high adjusted NT-ProBNP and high creatinine were significantly associated with higher mortality. Multivariable analysis identified pre-existing AF (HR 1.90 [CI 1.07-3.38], $p=0.03$), dialysis (HR 5.54 [CI 1.03-29.87], $p<0.05$) and cardiomyopathy (HR 2.64 [CI 1.40-4.95], $p<0.01$) as independent predictors (Table 10).

Table 10. Univariable and multivariable analyses.

	univariable analysis	multivariable analysis	
	p	HR (95% CI)	p
predictors of NOAF (n=226)			
previous valve surgery	0.08	5.86 (1.04-32.94)	<0.05*
baseline haemoglobin	0.06		
predictors of 1-year-mortality (n=398)			
cardiomyopathy	<0.01*	2.64 (1.40-4.95)	<0.01*
pre-existing AF	0.02*	1.90 (1.07-3.38)	0.03*
adjusted NT-proBNP (n=368)	<0.01*		<0.05*
periphery arterial disease	0.02*		
albumin (n=290)	0.04*		
baseline creatinine	<0.05*		
left bundle branch block	0.08		

**: p<0.05. Reproduced from Zweiker et al. (113) with permission of publisher Elsevier (see Disclosures section for details).*

3.4 Austrian LAAC Registry

3.4.1 Methods

The Austrian LAAC Registry (NCT03409159) is a prospective registry with the goal to document every LAAC procedure in Austria. The registry has been approved by the ethics committee of the Medical University of Graz (29-355 ex 16/17). The current study includes all patients with LAAC procedures until the end of 2017 in all currently active centres in Austria. We already published this analysis recently (116).

3.4.1.1 Recruitment and indications

Patients were recruited based on clinical practice guidelines (23) and the discretion of the treating physician. Based on the patients' individual history, patients were stratified by three main indications to perform LAAC. All patients with a history of major bleeding were stratified into the *bleeding* group, while patients with a history of cerebral or peripheral thromboembolism were summarized into the *thromboembolism* group. Residual patients were pooled into the *other* group. In patients with both bleeding and thromboembolism events, adjudication was based on the final event leading to the decision to perform LAAC.

3.4.1.2 Procedure

Patients received either Watchman™ (Boston Scientific, Marlborough, MA, USA), Amplatzer Cardiac Plug™ (Abbott Laboratories, North Chicago, IL, USA) or Amplatzer Amulet™ (Abbott Laboratories) devices. Device selection and procedures were performed based on local and international policies.

3.4.1.3 Antithrombotic treatment

Post-procedural antithrombotic treatment was usually based on international recommendations and risk assessment of individual patients.

3.4.1.4 Follow-up

Follow-up visits were performed on the discretion of the individual centre, but normally included TOE after 3-6 months and regular visits further on. All follow up visits until December 31st, 2017 were included into the analysis.

3.4.1.5 Data collection

We assessed parameters as recommended by the EHRA/EAPCI consensus statement on LAAC (117). Data were collected either by a local representative or an external reviewer. In addition to the hospital's local health records, we gathered data of readmissions at other hospitals after LAAC. Mortality data was verified by the Austrian government's population registry (118). Loss of follow up was defined as either last clinical visit or last day of available survival data.

3.4.1.6 Endpoints

We defined *procedural major complications* as any complications requiring invasive intervention or surgery, remaining complications were summarized as *procedural minor complications*. *Cardiac tamponade* was defined as acute pericardial effusion requiring pericardiocentesis or surgery. *Access site complications* were only reported as such if any invasive intervention would be necessary. We defined *ischaemic stroke* only in symptomatic patients according to current guidelines. *Shock* was defined as hypotension with the requirement for catecholamine therapy; *acute kidney injury* was reported if serum creatinine rose by ≥ 1.5 times from baseline within < 7 days. At long-term follow-up:

bleeding, *stroke* or *embolism* were counted if there was the requirement for rehospitalization. We summarized any rehospitalization that was adjudicated a direct consequence of the LAAC procedure or that was caused by a malfunctioning of the LAAC device as *hospitalization due to LAAC*.

Residual flow was defined as any colour doppler flow > 1 mm detected by TOE and stratified to *minor flow* (1 – 5 mm) and *major flow* (> 5 mm).

3.4.1.7 Statistical analysis

IBM SPSS (IBM, Armonk, NY) was used for data analysis. We expressed results as count (proportion), mean ± standard deviation or median (interquartile range, IQR). For bivariate analysis, we compared parameters between all three groups by ANOVA (in normally distributed values, based on Kolmogorov-Smirnov-Z test) or Kruskal-Wallis test. In case of significant interaction, we performed post-hoc testing using Fisher's LSD or Kruskal-Wallis test. For categorial values, Fisher's exact test was used. If appropriate, p values were adjusted according to Bonferroni correction. Distinct p values in the text refer to between-group differences.

The estimated number of bleeding and stroke events based on individual CHA_2DS_2-VASc and HAS-BLED scores were calculated based on data of Olesen et al (119, 120) as outlined by LaHaye et al (121), using the adjusted score (instead of the reported score). Based on the risk of individual patients, the estimated number of thromboembolic and bleeding events per patient-year for the whole population was calculated and compared to the observed event rate.

3.4.2 Results

A total of 186 LAAC procedures were incorporated into this analysis (Figure 14). This represents 98.9% of all procedures performed during this period. Two patients had to be excluded because relevant data was not provided by the implanting centre, which is currently inactive. The median age was 75 (IQR, 70-79) years and 37.6% were female. Baseline characteristics are shown in Table 11.

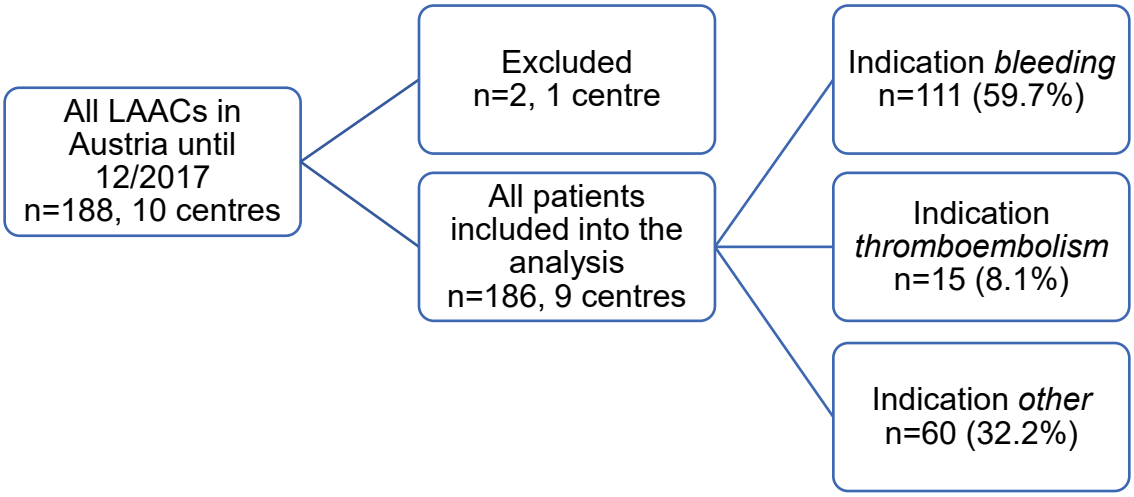


Figure 14. Study flowchart. LAAC: left atrial appendage closure.

Table 11. Baseline characteristics of treated patients grouped by indication for LAAC. LAAC: left atrial appendage closure.

parameter	indication for LAAC			p value	
	bleeding	thromboembolism	other	overall	post-hoc
number of patients	111	15	60	N/A	
female	38.7%	20.0%	40.0%	0.355	
age (years)	74 (70-78)	74 (62-76)	77 (72-81)	0.029	§
body mass index, kg m^{-2}	26 (24-30)	25 (22-30)	27 (24-31)	0.409	
CHA_2DS_2-VASc score	4.6±1.4	4.8±1.2	4.2±1.5	0.150	
$CHADS_2$ score	2.8±1.2	3.8±0.7	2.5±1.2	<0.001	**,‡‡
HAS-BLED score	3.6±0.7	2.9±0.6	2.9±0.9	<0.001	**,††
congestive heart failure	27.9%	6.7%	11.7%	0.017	§
arterial hypertension	86.5%	86.7%	90.0%	0.780	
diabetes mellitus	25.2%	40.0%	28.3%	0.462	
transitory ischemic attack, stroke or thromboembolism	47.7%	100.0%	28.3%	<0.001	**,†,‡‡
vascular disease	42.3%	20.0%	38.3%	0.270	

parameter	indication for LAAC			p value	
	bleeding	thromboembolism	other	overall	post-hoc
uncontrolled hypertension	9.0%	0%	8.3%	0.762	
abnormal renal function	15.3%	6.7%	13.3%	0.803	
abnormal hepatic function	1.8%	0%	6.8%	0.240	
stroke	40.5%	93.3%	18.3%	<0.001	**,†,‡‡
history of bleeding	100.0%	26.7%	45.0%	<0.001	**,††
labile International Normalized Ratio values	2.7%	6.7%	1.7%	0.453	
alcohol abuse	2.7%	0%	3.2%	0.655	
coronary artery disease	45.0%	6.7%	50.0%	0.006	*,‡‡
cerebral artery disease	15.0%	13.3%	10.9%	0.837	
periphery artery disease	7.2%	13.3%	5.0%	0.389	
history of percutaneous intervention	22.5%	0%	31.7%	0.021	‡
history of coronary artery bypass grafting	13.5%	6.7%	5.0%	0.200	

parameter	indication for LAAC			p value	
	bleeding	thromboembolism	other	overall	post-hoc
chronic obstructive pulmonary disease	18.2%	6.7%	7.3%	0.133	
dialysis	1.0%	0%	0%	1.000	
hyperlipoproteinemia	35.4%	64.3%	29.1%	0.059	
paroxysmal AF	27.6%	26.7%	42.6%	0.165	
laboratory results					
haemoglobin, g/dL	12.9±2.0	14.6±1.3	12.6±1.9	0.002	**,‡‡
NT-proBNP, mg/dL	979 (433-1913)	618 (486-1464)	755 (275-1528)	0.534	
creatinine, mg/dL	1.1 (1.0-1.4)	1.1 (1.0-1.2)	1.1 (1.0-2.3)	0.339	
echocardiography					
left-ventricular function 35-50% <35%	 16.2% 13.5%	 6.7% 12.7%	 13.3% 6.7%	0.659	
patent foramen ovale	9.9%	20.0%	11.7%	0.510	

parameter	indication for LAAC			p value	
	bleeding	thromboembolism	other	overall	post-hoc
LAA minimum orifice diameter, mm (n=58)	17.0±4.3	19.5±2.7	16.1±3.7	0.277	
LAA maximum orifice diameter, mm (n=58)	20.8±4.6	23.0±3.2	19.3±4.1	0.222	
baseline medication					
VKA	9.0%	6.7%	20.0%	0.104	
DOAC	23.4%	80.0%	28.3%	<0.001	**,‡‡
aspirin	19.8%	13.3%	31.7%	0.155	
adenosine diphosphate receptor inhibitor	13.5%	0%	14.0%	0.190	
low molecular weight heparin	25.2%	6.7%	25.0%	0.303	
dual antiplatelet therapy	6.3%	0%	13.3%	0.177	

*The following symbols represent significant differences in post-hoc testing (after Bonferroni adjustment): bleeding vs embolism: * $p<0.05$, ** $p<0.01$; bleeding vs other: † $p<0.05$, †† $p<0.01$; embolism vs other: ‡ $p<0.05$, ‡‡ $p<0.01$; § no significant interaction in post-hoc testing found. Reproduced from Zweiker et al (116) licensed under CC BY.*

3.4.2.1 Indications

The majority of patients (59.7%) had a history of bleeding (*bleeding* group), with most of the patients having suffered intracranial bleeding (31.7%, Figure 15). Patients with intracranial bleeding had intracerebral haemorrhage (23.7%), subdural haematoma (5.4%), subarachnoid bleeding (4.3%) or epidural haemorrhage (0.5%). Gastrointestinal bleeding was prevalent in 19.9%, followed by epistaxis (0.5%) or other types of bleeding (7.0%). The majority of patients had their bleeding while being on OAC (42.3%), either having received VKA or DOACs (28.85% each).

A proportion of patients (8.1%) received LAAC because of a history of thromboembolism despite OAC (*thromboembolism* group); they had either had a stroke (7.0%) or peripheral thromboembolism (1.1%).

The third indication group (*other* group) comprised 32.2% of patients. Of patients with predisposition for bleeding (7.0%), 2.2% had a gastrointestinal malformation, 1.6% had Morbus Osler and 1.1% had a cerebral malformation. Further indications were intolerance to OAC without major bleeding (4.8%), anaemia of unknown cause (4.3%) and contraindications to OAC (4.3%). Another 4.3% received LAAC due to refusal of lifelong OAC and 4.3% had LAAC prior to PCI to avoid triple antithrombotic therapy in cases with high bleeding risk. In one patient, LAAC was performed to seal a previously performed surgical left appendage exclusion.

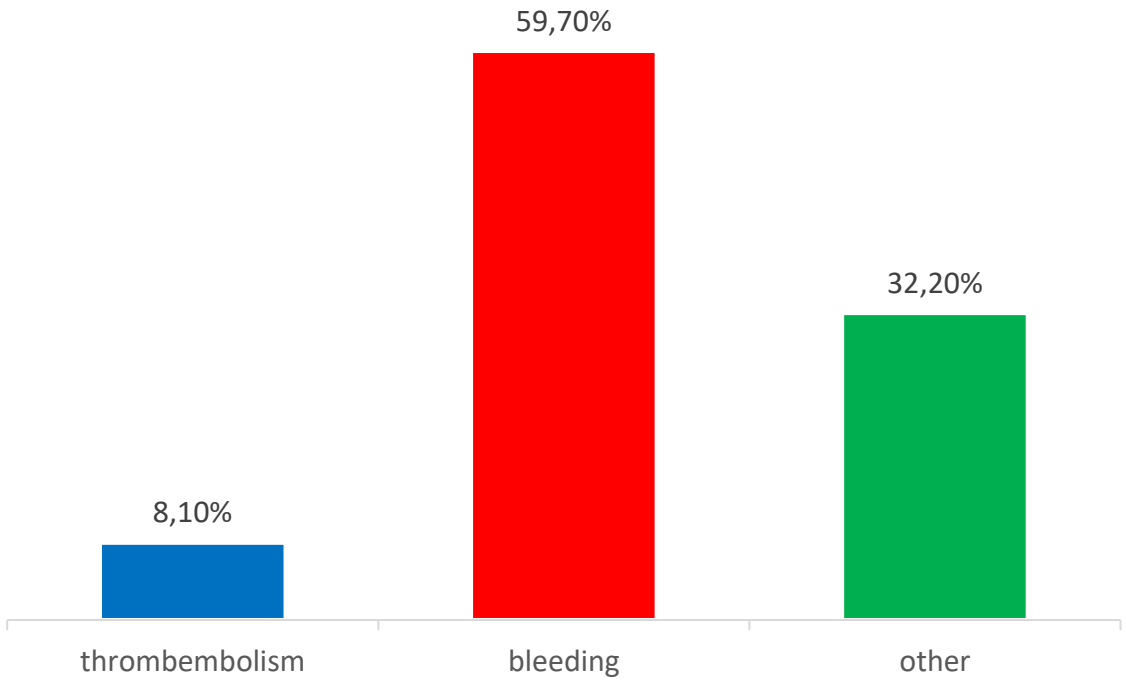


Figure 15. Indications for LAAC. LAAC: left atrial appendage closure.

3.4.2.2 Basic risk profile

The overall cohort had a mean CHA_2DS_2-VASc score of 4.5±1.4, a $CHADS_2$ score of 2.8±1.2 and a HAS-BLED score of 3.3±0.9 (Table 11). There significant differences of risk profiles in the pre-specified groups.

The HAS-BLED score was highest in the *bleeding* group ($p<0.005$ vs. remaining groups) due to a more prevalent history of bleeding (100% vs. *thromboembolism* group 26.7% vs. *other* 45.0%, $p<0.001$).

$CHADS_2$ score was highest in the *thromboembolism* group ($p<0.001$ vs. remaining groups), which was caused by a significantly higher prevalence of stroke (93.3% vs. 18.3%, $p<0.001$).

The rate of coronary artery disease was significantly lower in *thromboembolism* patients (6.7%) compared to remaining groups ($p<0.05$ for both). Patients in the *other* group had the lowest prevalence of the factor *transitory ischaemic attack, stroke or thromboembolism* of the CHA_2DS_2-VASc score (28.3% vs. *bleeding* patients 47.7% vs. *thromboembolism* patients 86.7%). Consequently, $CHADS_2$ and HAS-BLED scores were lowest in those patients.

3.4.2.3 Antithrombotic treatment before LAAC

Before LAAC, 42.0% received OAC in the total cohort (42.0%; DOAC, 29.6%; VKA, 12.4%, Table 11). Other therapies were low molecular weight heparin (23.7%), aspirin (23.1%), P_2Y_{12} inhibitors (mostly clopidogrel, 14.0%) or dual antiplatelet therapy (8.1%). DOAC therapy before LAAC was most prevalent in the *thromboembolism* group (80.0%, vs. *bleeding* group, 23.4%; *other* group, 28.3%, $p<0.01$).

3.4.2.4 Procedure

The LAAC procedure was performed exclusively in 85.7%. Otherwise, it was combined with closure of a patent foramen ovale in 10.7%, which was performed most often in the *thromboembolism* group (26.7%) compared to the *bleeding* group (7.1%) and the *other* group (12.7%, Table 12). Other concomitant procedures were transcatheter mitral-valve repair (1.8%) or coronary angiography and/or percutaneous coronary intervention (1.8%). The Amplatzer Cardiac Plug or Amplatzer Amulet devices were used in 52.2% and the Watchman device in 46.8%. Devices with a median diameter of 25 (IQR, 24-27) mm were used.

3.4.2.5 Procedural outcome

First procedure success for LAAC implantation was 97.3%. In the remaining cases, implantation was not possible due to technical difficulties (1.6%), intra-procedurally detected LAA thrombus (0.5%) or dislocation due to left atrial appendage anatomy (0.5%). Median duration of the procedure was 70 minutes (range, 20 minutes to 3.5 hours). Fluoroscopy was used for a median of 15 (IQR, 11-23) minutes and 100 (66-148) mL of contrast dye were used, without significant differences between groups.

The rate of major complications was 7.0%, including cardiac tamponade (3.2%), access site complication (2.2%), ischaemic stroke (1.1%) and shock requiring catecholamines (1.1%). There were no significant differences in procedural outcome between groups and in-hospital mortality was 0%.

Table 12. Procedural outcome and follow-up echocardiography.

parameter	indication for LAAC			p value
	bleeding	thromboembolism	other	
technical details				
LAAC only	89.8%	73.3%	81.8%	0.113
concomitant PFO closure	7.1%	26.7%	12.7%	0.055
concomitant transcatheter mitral-valve repair	1.0%	0.0%	3.6%	0.467
concomitant coronary angiography +/- percutaneous intervention	3.1%	0.0%	0.0%	0.663
implanted device				0.038 §
Amplatzer™	47.7%	86.7%	51.7%	
Watchman™	50.5%	13.3%	48.3%	
other/none implanted	1.8%	0.0%	0.0%	
size, mm	25 (24-27)	25 (22-28)	25 (22-28)	0.743
outcome				
primary implantation success	97.3%	100.0%	96.7%	1.000
minor residual flow	3.6%	0.0%	3.3%	1.000

parameter	indication for LAAC			p value
	bleeding	thromboembolism	other	
procedure time, min (n=109)	65 (51-89)	60 (55-65)	86 (60-110)	0.088
procedure time without concomitant procedures, min (n=73)	64 (51-95)	65 (55-182)	85 (64-96)	0.366
dose area product, µGym² (n=117)	4220 (1058-8901)	8319 (6052-10428)	6929 (1218-12485)	0.149
fluoroscopy time, min (n=123)	15 (11-24)	14 (11-32)	17 (12-22)	0.795
amount of contrast, mL (n=148)	96 (64-146)	106 (70-145)	106 (66-154)	0.595
hospitalization duration, days (n=168)	3 (2-5)	2 (2-6)	3 (2-7)	0.225
procedural major complication	4.5%	13.3%	10.0%	0.159
cardiac tamponade	2.7%	6.7%	3.3%	0.512
access site complication	1.8%	6.7%	1.7%	0.376
ischemic stroke	0.0%	0.0%	3.3%	0.258
shock	0.9%	0.0%	1.7%	1.000

parameter	indication for LAAC			p value
	bleeding	thromboembolism	other	
cardiac arrest	0.9%	0.0%	0.0%	1.000
procedural minor complication	9.9%	13.3%	16.7%	0.443
unplanned admission to intensive care unit	4.5%	6.7%	6.7%	0.679
bleeding requiring blood transfusion	0.9%	0.0%	8.3%	0.030 §
acute kidney injury	0.9%	0.0%	3.3%	0.443
echocardiography at follow up				
duration to TOE, days (n=111)	96±58	69±27	103±99	0.487
residual flow (n=110) major minor	1.5% 0.0% 1.5%	0.0% 0.0% 0.0%	2.8% 0.0% 2.8%	1.000
thrombus (n=108)	1.5%	0.0%	2.9%	1.000

§ *no significant interaction between groups has been found in post-hoc testing. Reproduced from Zweiker et al (116) licensed under CC BY.*

3.4.2.6 Antithrombotic treatment after LAAC

After LAAC, most patients (52.7%) received dual antiplatelet therapy (mostly aspirin plus clopidogrel) for 1-6 months after LAAC (Table 13). OAC was prescribed in 19.9% (DOAC, 14.0%; VKA, 5.9%). For OAC, phenprocoumon (17.1%), apixaban (46.4%, dabigatran (35.7%) and rivaroxaban (17.9%) were used. OAC prescription was most prevalent in the *thromboembolism* group (53.3%). Other options for antithrombotic treatment were aspirin (7.5%), clopidogrel (5.4%) or no antithrombotic therapy at all (12.4%).

After a median of 3 (IQR 2-6) months, 43.5% switched to aspirin as long-term therapy. In 39.2%, no further antithrombotic therapy was given. OAC was only continued in 4 patients (26.7%) of the *thromboembolism* group (DOAC, 20.0%; VKA, 6.7%). Long-term antithrombotic therapy could not be assessed in 15.1% of patients.

Table 13. Post-procedural anticoagulation strategy. DAPT: double antiplatelet therapy, DOAC: direct oral anticoagulant, LMWH: low molecular-weight heparin, SAPT: single antiplatelet therapy, VKA: vitamin K antagonist.

parameter	indication for LAAC			p value
	bleeding	thrombo-embolism	other	
early antithrombotic therapy				
duration, months (n=160)	3 (2-6)	3 (3-6)	3 (3-6)	0.309
DAPT	47.7%	46.7%	63.3%	0.131
oral anticoagulation	17.1%	53.3%	16.7%	0.008 *,‡
DOAC alone	12.6%	20.0%	8.3%	
VKA alone	4.5%	0.0%	1.7%	
DOAC + SAPT	0.0%	20.0%	1.7%	
VKA + SAPT	0.0%	13.3%	5.0%	
SAPT	18.9%	0.0%	11.7%	0.114
Aspirin	10.8%	0.0%	3.3%	
Clopidogrel	4.5%	0.0%	8.3%	
Aspirin + LMWH	2.7%	0.0%	0.0%	
Clopidogrel + LMWH	0.9%	0.0%	0.0%	
no antithrombotic therapy	16.2%	0.0%	8.3%	0.112
long-term antithrombotic therapy				

parameter	indication for LAAC			p value
	bleeding	thrombo-embolism	other	
SAPT	42.3%	33.3%	48.3%	0.560
Aspirin	36.0%	26.7%	45.0%	
Clopidogrel	6.3%	6.7%	3.3%	
no antithrombotic therapy	40.5%	33.3%	38.3%	0.869
oral anticoagulation	0.0%	26.7%	0.0%	<0.001 **,‡‡
DOAC	0.0%	20.0%	0.0%	
VKA	0.0%	6.7%	0.0%	
other / not documented	17.1%	6.7%	13.3%	0.592

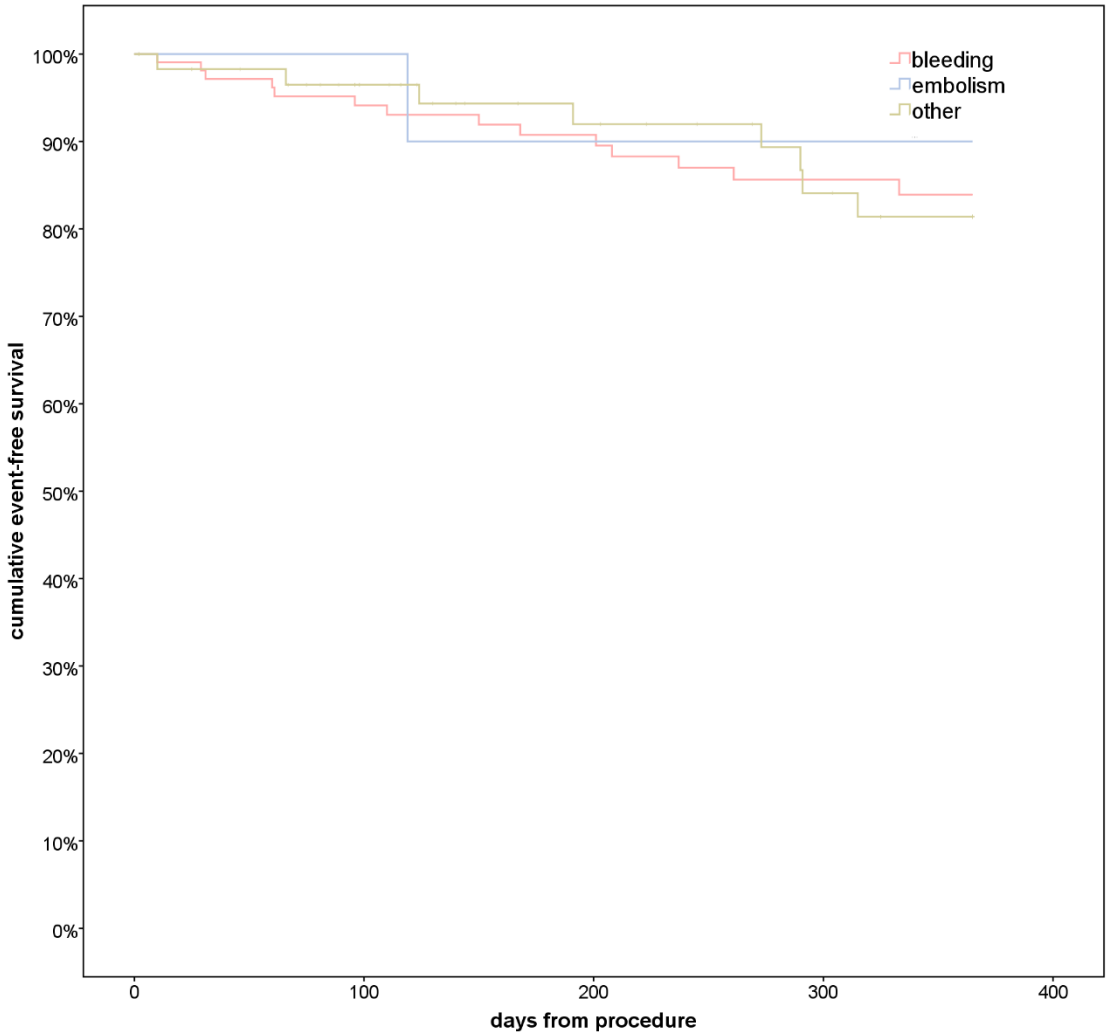
*The following symbols represent significant differences in post-hoc testing (after Bonferroni adjustment): bleeding vs embolism: * p<0.05, ** p<0.01; bleeding vs other: † p<0.05, †† p<0.01; embolism vs other: ‡ p<0.05, ‡‡ p<0.01; § no significant interaction in post-hoc testing found. Reproduced from Zweiker et al (116) licensed under CC BY.*

3.4.2.7 Follow up

Documentation of follow-up TOE 96±73 days after the LAAC procedure was available in 59.7% of patients. TOE confirmed correct position of the LAAC device without major residual flow in 98.9%. In one patient, the LAA device could not be found in the LAAC but in a pulmonary vein and in another patient major residual flow of 6mm was determined. Minor residual flow was prevalent in 1.8% and a device-associated thrombus was found in 1.9% of patients.

Long-term follow up was 477±464 days and 85.5% of patients reached a follow-up of > 90 days. The combined 1-year endpoint of death, stroke, bleeding or LAAC-associated hospitalization occurred in 16.5% of patients without significant differences between groups (Table 14). During total follow-up, all-cause mortality of 11.3% was documented, with one-year survival in 83.9%, 90.0% and 81.4% in *bleeding*, *thromboembolism* and *other* groups, respectively (Figure 16). Stroke or peripheral thromboembolism occurred in 4.8% and bleeding in 7.0%. Ischaemic stroke occurred in 1.6% of patients. Patients with stroke or peripheral thromboembolism after LAAC were on single antiplatelet therapy in 55.6%, had no antithrombotic therapy in 33.3% or dual antiplatelet therapy in 11.1% at the time of event. Bleeding occurred while patients were taking single antiplatelet therapy (46.2%), dual antiplatelet therapy (30.8%) or no antithrombotic therapy (23.1%).

Figure 16. Kaplan Meier plot of cumulative survival of patients after LAAC, stratified by subgroup. LAAC: left atrial appendage closure.



LAAC-associated rehospitalization was 1.6%, due to Dressler's syndrome, a large device thrombus (which was dissolved by low molecular weight heparin therapy) and the necessity to remove a free-floating LAAC device surgically from the pulmonary vein (n=1, 0.9% each).

parameter	indication for LAAC			p value
	bleeding	thromboembolism	other	overall
follow-up duration, days	474±449	268±203	535±525	0.178

combined endpoint (1-year death, stroke, bleeding or LAAC-associated hospitalization)	16.1%	10.0%	18.6%	0.891
death	9.0%	6.7%	16.7%	0.253
bleeding	7.2%	0.0%	8.3%	0.668
stroke or thromboembolism	4.5%	0.0%	6.7%	0.762
ischaemic stroke	1.8%	0.0%	1.7%	1.000
hospitalization due to LAAC	0.9%	6.7%	1.7%	0.256
any hospitalization	28.8%	33.3%	30.0%	0.879

Table 14. Follow up after LAAC. LAAC: left atrial appendage closure. Reproduced from Zweiker et al (116) licensed under CC BY.

3.4.2.8 Predicted vs observed events

Based on individual CHA_2DS_2-VASc scores, we predicted a yearly rate of stroke or peripheral thromboembolism of 8.6%, which was highest in the *thromboembolism* group (9.6%). The actual event rate of 3.7% reflects a significant relative reduction of 57% compared to the predicted rate (p=0.035, Table 15).

Predicted bleeding rate based on individual HAS-BLED scores was 7.7% with highest risk in *bleeding* patients (8.3%). The observed bleeding rate of 5.3% corresponds to a relative risk reduction of 30% (p=0.454). The observed rate of both thromboembolic and bleeding events was highest in the *other* group and lowest in the *thromboembolism* group (Table 15).

Table 15. Mean predicted annual stroke and bleeding events (as by CHA_2DS_2-VASc and HAS-BLED scores) compared to reported events in the Austrian LAAC Registry. LAAC: left atrial appendage closure. Reproduced from Zweiker et al (116) licensed under CC BY.

parameter	all patients	indication for LAAC		
		bleeding	thromboembolism	other
annual embolic events				
predicted	8.6%	8.9%	9.6%	7.8%
observed	3.7%	3.5%	0.0%	4.5%
relative reduction	-57.0%	-61.0%	-100.0%	-42.0%
p value	0.035*	0.083	1.000	0.529
annual bleeding events				
predicted	7.7%	8.3%	6.6%	6.7%
observed	5.3%	5.5%	0.0%	5.7%
relative reduction	-30.2%	-33.2%	-100.0%	-15.6%
p value	0.454	0.483	1.000	1.000

4 Discussion

The results of the three studies give important insights in AF prediction, AF in TAVI patients and non-medicinal stroke prevention in AF patients. They all show a high prevalence of AF in different populations. The SAFE-ME study even assumes a higher rate of subclinical AF. The TAVI-AF study proves that the effect of AF on long-term outcome is not limited to increased risk of stroke and heart failure, and it is dependent on existing risk factors as all studies suggest. Therefore, patient-tailored therapy is necessary, with new possibilities emerging in the last years. The analysis of the Austrian LAAC Registry describes a new technology if OAC is not tolerated.

While all studies are related to AF in patients requiring cardiac interventions, they handle different aspects of AF and are therefore discussed in separate chapters.

4.1 AF prediction and the SAFE-ME study

While this analysis of the SAFE-ME study represents only an interim analysis without the application of the AF initiation algorithm, it gives important hints about AHRE in pacemaker patients: First, the incidence of AHRE was high in pacemaker patients. Second, there was no clear association between pre-existing AF and AHRE. Third, diabetes mellitus, pre-existing anticoagulation and previous AHRE were independent predictors for the development of AHRE at follow up.

4.1.1 Incidence of AHRE

In this analysis, 25.9% of included patients developed AHRE after a follow up of only 6 months. Previous studies documented higher proportions of AHRE in pacemaker patients without history of AF (28% to 35%) (8, 122, 123). However, those studies had a longer follow up (1-2.5 years) and they included a higher proportion of patients with sick sinus syndrome (25-50% vs. 13%) (8, 123) due to inclusion of patients with an atrial pacing rate > 50%. Studies exclusively analysing patients with sick sinus syndrome have shown an even higher incidence of AHRE episodes (50-68%) (124, 125). Two hypotheses have been proposed to explain the association between sinus nodal disease and AF (126): The higher probability of atrial extrasystoles during bradycardia facilitating re-entry and a similar pathophysiology of both disease entities (i.e., atrial wall disturbances, atrial ischemia).

4.1.2 Predictors of AHRE

Previous AHRE was the most significant predictor of AHRE at follow up in bivariable analysis. This fact highlights the importance of the recognition of AHRE as relevant arrhythmia that may recur at any time. As we found no correlation between the history of AF and AHRE, we postulate that short AHRE episodes may act rather as precursor than an

indirect sign of AF. Frequent AHRE episodes of long duration have already been shown to be associated with AF and atrial flutter (127).

Diabetes mellitus was also associated with the development of AHRE. The positive correlation between $CHADS_2$, CHA_2DS_2-VASc scores and its factors (such as diabetes mellitus) and AF are well-known in the literature (1). Wakula et al validated those risk factors for the development of AHRE in pacemaker patients and additionally found NT-proBNP among other less-used biomarkers to be significant predictors (64).

4.1.3 Limitations

The fact that this is an interim analysis and the limited number of included patients affects the power analysis and might lead to an underestimation of risk factors that may appear more significant when the analysis includes a larger patient population. Furthermore, the AF initiation score was not applied. However, these limitations will likely be overcome once the study is finalized.

4.1.4 Outlook

As the SAFE-ME project is an important step forward in the validation of a novel ECG algorithm for the prediction of AF, it will be prolonged until the necessary number of patients is included. The next logical step after completion of the SAFE-ME study is to test the AF initiation score in different patient populations and develop it further. If this algorithm, combined with clinical parameters, proves to be effective, a simple Holter ECG could potentially allow for AF prediction 6 months in advance for CIED patients. This would be a cost-effective alternative to more invasive and expensive diagnostic tools (such as long-term event monitors). Furthermore, anticoagulation therapy could be initiated in patients with previously unknown AF. As the prevalence of AF increases in our ageing

population, such algorithms and clinical decision tools will become even more important in the future.

The SAFE-ME study observes the development of AHRE instead of AF (which, by definition, has to be diagnosed with surface ECG) (1). Therefore, its clinical relevance is partly dependent on the results of ongoing trials, which investigate the effectiveness of anticoagulation in AHRE patients without the diagnosis of AF on the surface ECG (128, 129). The NOAH-AFNET study represents one of them and is currently conducted in the Medical University of Graz (128).

4.2 AF, TAVI and the AF-TAVI study

The main findings of the AF-TAVI study are the following: (1) Pre-existing AF was an independent predictor of one-year mortality after TAVI, (2) the incidence of NOAF was low (7%), and (3) NOAF patients had higher morbidity but not higher mortality than patients in sinus rhythm.

The strength of this study is the inclusion of many well-characterized patients with complete 1-year follow up. We achieved a high data quality due to extensive investigation. The detailed data from the registry enabled us to analyse a large number of parameters. As well-established rhythm-monitoring protocols had been included, it was possible to detect NOAF patients with a high level of certainty.

4.2.1 Patient cohort

With a median age of 82 years and a median EuroSCORE II of 5.9%, this patient cohort represents a typical TAVI cohort. Characteristics were comparable to studies published from other contemporary TAVI registries at that time (93, 130).

The prevalence of pre-existing AF (43%) in our study was substantially higher than expected in a standard population with a similar age (131), partly because patients underwent extensive monitoring during recruitment for TAVI (132). Pre-existing AF (43%) was also more frequent than in other studies examining the effects of TAVI, such as a meta-analysis of Sannino et al (133) including 14,078 patients (pre-existing AF rate 33%). In line with Chopard et al (93), comorbidities were significantly more prevalent in the pre-existing AF group, leading to a higher procedural risk.

4.2.2 Risk scores for TAVI patients

Before the introduction of TAVI-tailored and well-accepted risk scores (134), patients' risk was estimated by scores derived from surgical valve replacement procedures (i.e. EuroSCORE, EuroSCORE II and STS Risk Score). These are the only scores recommended by international guidelines (135, 136), although they might over-estimate 30-day mortality (especially logistic EuroSCORE (115)). Two scores with regard to TAVI patients have already been published at time of this analysis, but they lack external validation and broad acceptance (137, 138). We included one of them, namely the German AV Score, but it did not predict 1-year mortality in our patient cohort. The new STS/ACC risk model was developed after the publication of this analysis(139). While those scores predict short-term outcome very well, they failed to predict long-term survival in our cohort.

4.2.3 Predictors of mortality

We suggest that pre-existing AF is a major risk factor in TAVI patients. We showed that 1-year mortality in patients with pre-existing AF was almost twice as high after correction for other confounders. Furthermore, long-term complications, such as cardiac rehospitalizations and cardiovascular mortality, but not stroke were more common in pre-existing AF patients. It is unclear, whether AF itself (by the reduction of cardiac output and chronotropic incompetence) increases morbidity and mortality in those patients, or AF serves as surrogate marker for other cardiac conditions associated with a higher risk. A recent report suggests that AF itself is not an independent predictor of outcome if other factors (for instance, left atrial volume) are considered (95). Nevertheless, cardiac events may play a more important role rather than cerebrovascular events in this cohort of patients. Chopard et al. and Biviano et al. showed similar results (93, 140). Sannino et al

demonstrated elevated long-term all-cause mortality in patients with pre-existing AF (133). They also demonstrated that pre-existing AF was associated with long-term cardiovascular mortality but not with long-term cerebrovascular events. However, most of the data included in this meta-analysis have not been adjusted for other confounders. Although persistent AF might be a stronger risk factor than paroxysmal AF (141), screening for intermittent arrhythmias is especially important before TAVI evaluation of risk. The STS risk score and German AV score have included pre-existing AF in their risk analysis.

In addition to AF, end-stage renal disease requiring dialysis and cardiomyopathy were independent risk factors of elevated 1-year mortality.

4.2.4 NOAF

In our cohort, the incidence of NOAF (7%) was lower than in most of other analyses, which report a prevalence of 2 to 39% (133, 142). As Tanawuttiwat et al. demonstrated higher incidences of NOAF in patients receiving TAVI with pericardiotomy (143), the high incidence of transfemoral approach (94%) may explain this difference. A large registry study reported a lower incidence of NOAF (93), but without any information on patient's monitoring after the procedure. Therefore, silent episodes of paroxysmal AF could have been left undiagnosed and untreated in this study.

The prediction of patients developing NOAF after TAVI remains difficult. Rhythm monitoring is essential after the procedure. Previous valve surgery was the only independent risk factor for NOAF in our analysis, which was present in 13% of NOAF patients. While postoperative AF is common after heart surgery (144), there is insufficient data to determine if this effect persists even years after surgery. Left atrial diameter was only numerically higher in NOAF patients, but we did not find any significant difference in

diameter between NOAF and no-NOAF patients which confirms findings published by Amat-Santos et al. (145).

In our study, two percent of previous no-NOAF patients developed AF after discharge in the first post-procedural year. This underlines the importance of regular follow up including ECG monitoring after TAVI.

Recent studies report a contradictory effect of NOAF on long-term mortality (93, 96, 133). Except for two studies using questionable NOAF detection methods (93, 140), NOAF was associated with higher long-time morbidity, but not mortality (133, 146). We report a numerically longer ICU stay, and elevated rates of cardiac rehospitalization and out-of-hospital stroke in NOAF patients. Intrahospital events were also more common in the NOAF group (44% vs. pre-existing AF 34% vs. no NOAF 30%), but differences between groups were not statistically significant. These results highlight the importance of identifying NOAF as special condition predicting increased probability for events.

New data highlights the importance of thorough screening before TAVI: Asmarats et al found new AF using 1-week Holter monitoring in 10.1% of patients before undergoing TAVI (147).

4.2.5 Limitations

Like every retrospective analysis, this report is also prone to limitations such as confounding and information bias. However, we tried to minimize selection bias by recruiting all TAVI patients within a pre-specified time interval. However, the results of this study may not be generalizable to all consecutive TAVI cohorts, because only Core-Valve prostheses were implanted and in most patients the valve was implanted via the

transfemoral access. After the initial phase of telemetry for 48 hours, patients were not monitored continuously (e.g., by implantable loop recorders).

4.2.6 Summary of other TAVI-related studies

The AF-TAVI study was the first step in the development of a solid database of TAVI patients of the Medical University of Graz. This database formed the basis of several individual projects that were conducted during the doctoral studies and are described here briefly.

Several investigations concentrated on specific factors of TAVI patients at Graz, e.g. the association of outcome with biomarkers (148, 149), right heart haemodynamics from preprocedural MRI (Schmid et al, under review) and frailty (Gharibeh et al, in preparation). In a multicentric study led by Pagnesi et al from San Raffaele Hospital (Milan, IT) two next-generation TAVI prostheses were compared (150, 151). A multicentre analysis analysing the predictive value of invasive haemodynamic measurements on long-term outcome is currently conducted.

The Austrian TAVI Registry, which was also developed by the Department of Cardiology, Medical University of Graz could describe early success of TAVI in Austria in 2013 (152). The registry was the basis of a propensity score matched analysis led by the Medical University of Graz and the Klinik Ottakring, which compared the outcome of 1822 patients undergoing TAVI at on-site cardiac surgery vs. non on-site cardiac surgery centres (153). This analysis concluded that patients undergoing TAVI in centres without on-site cardiac surgery had a higher baseline risk and consecutively a worse outcome post TAVI. After matching for baseline factors, the difference between centres with vs. without on-site cardiac surgery disappeared.

4.3 AF, non-medicinal stroke prevention and the Austrian LAAC registry

These are the main findings of this analysis of the Austrian LAAC registry: First, LAAC was performed in a heterogeneous patient population with varying individual risk profiles. Second, there was a considerable risk of procedural complications during or after the LAAC procedure, but all complications could be managed successfully. Third, observed long-term rates of thromboembolism and bleeding were lower than predicted based on individual risk profiles using CHA_2DS_2-VASc and HAS-BLED scoring.

4.3.1 Indications for LAAC

With a mean CHA_2DS_2-VASc score of 4.5 and a mean HAS-BLED score of 3.3, all patients receiving LAAC in Austria had an elevated risk of thromboembolism and bleeding as estimated by validated scores. Therefore, LAAC was a considerable option in all patients.

LAAC is currently indicated as second line therapy to prevent thromboembolic events. A specific index event or condition usually leads to the decision to perform LAAC. This fact is especially important in Austria, because only a limited number of LAAC procedures are reimbursed by social security. As a result, the patient's characteristics and indications to perform LAAC are very well documented. While bleeding events in the past were the main indication in almost 60% of patients, reasons to perform LAAC in remaining patients were very heterogeneous and included predispositions for bleeding, refusal of OAC or even the requirement for triple antithrombotic therapy for limited time in case of planned percutaneous coronary intervention. A noteworthy indication is the occurrence of thromboembolic events while being on OAC.

Except for two studies (154, 155), thromboembolic risk of patients in this analysis as predicted by CHA_2DS_2-VASc score (median 5) and $CHADS_2$ score (median 3) was higher than in previous studies that report a CHA_2DS_2-VASc score of 4 (106, 108, 109, 156-160) or a $CHADS_2$ score of 2 (105, 161). With a median HAS-BLED score of 3 bleeding risk was comparable to published literature (109, 157-160).

To the authors' knowledge, this is the first study investigating the specific indications to perform LAAC and stratifying patients based on the indication. There is only scarce data reported in available literature. History of bleeding ranges from 72% to 93% in four multi-centre registries (155, 156, 158, 162). The EWOLUTION registry reports a history of haemorrhage in 31% (108). Patients with a history of stroke while being on OAC were partly included in the study of Kefer et al without giving distinct numbers (157) and exclusively analysed by Freixa et al (163). With 27.1%, patient choice was a common indication for LAAC in the German LAARGE registry (162). In two randomized controlled trials (105, 106), patients without contraindication to OAC only were included.

4.3.2 Procedural outcome

Both Amplatzer and Watchman devices were implanted successfully almost equally in Austria (52.2% vs. 46.8%). Understandably, concomitant closure of patent foramen ovale was performed most frequently in the *thromboembolism* group, to combine the benefit of both techniques within the same session.

With major complications occurring once every 14 procedures, LAAC must be considered a risky procedure in a high-risk population. The most common major complication was cardiac tamponade. We observed two ischaemic strokes during the LAAC procedure. There were no differences in rates of complications between the different indication groups.

The high incidence of complications might be explained by the high-risk cohort undergoing LAAC. However, low operator experience has also to be taken into account, as centres performed only a median of 17 procedures during the observation period. Fortunately, procedural survival was 100% and all complications were managed successfully during the hospital stay.

In comparison to other studies, implantation success rate of 97.3% was similar to other studies that included with Watchman (105, 106, 108, 156, 161) or Amplatzer (109, 155, 157-160) devices. A success rate of 90.9% (105) to 99.1% (160) has been reported. The frequency of major complications reported in the literature was also comparable, ranging from 2.2% (159) to 12.0% (157).

4.3.3 Post-procedural antithrombotic treatment

We documented a high variety of antithrombotic treatment after LAAC as the medication was tailored in accordance to the patient's individual history and left to the discretion of the physician in charge of those patients (Table 13). Most of the patients received dual antiplatelet therapy for the first couple of months after LAAC (52.7%), which was later switched to monotherapy with aspirin (43.5%) or no therapy (39.2%).

Patients in the *thromboembolism* group mostly stayed on OAC for the first months. Interestingly, in 73.3% of patients in the *thromboembolism* group no long-term OAC was described, and still no ischaemic event was documented at follow-up.

The majority of published studies, dual antiplatelet therapy was recommended for months 1-6 (109, 155-158, 160), followed by aspirin for 3 months (109, 158) or indefinitely (155-157). In PROTECT AF and PREVAIL studies (105, 106), Warfarin was used for the first 45 days.

4.3.4 Long-term outcome

Device-related complications were rarely detected at follow-up TOE at our study, with residual flow occurring in 1.8% and thrombus formation in 1.9%. Rehospitalizations due to the LAAC device itself was also rare (1.7%), and the LAAC device was dislocated in only one patient. Fortunately, the device did not follow the blood stream and was found immobile in the pulmonary vein. Further investigation excluded the possibility that the device was primarily implanted at the wrong site.

Within the first year after LAAC, the combined endpoint for death, stroke, peripheral thromboembolism, bleeding or LAAC-associated hospitalization was reached in 16.5% of patients. One explanation for this high long-term complication rate is the high baseline risk of the LAAC cohort. When comparing the individual predicted thromboembolic and haemorrhagic events with observed events, we experienced a reduction of 57.0% of thromboembolic events and a reduction of 30.2% of bleeding events.

The most pronounced reduction of events was reported in the *thromboembolism* group, which had no events at follow-up. This fact proves the effectiveness of LAAC in preventing thromboembolic events in the absence of OAC therapy (which was the case in almost 75% of patients in the *thromboembolism* group). However, the low sample size in the *thromboembolism* group limits further analyses.

The group with the highest rate of observed thromboembolic events (4.5%) and bleeding events (5.7%) despite moderate baseline risk was the *other* group. Consequently, the reduction of events compared to historic controls was lowest in this group. We propose two explanations for this finding: First, those patients may face risk factors for bleeding and thromboembolism that are not captured by traditional risk scores and therefore selected for LAAC. Second, LAAC may not be as effective in this patient group as in remaining

group. Further studies are needed to further examine this heterogeneous subgroup. Due to a rather small sample size, only the reduction of annual embolic events of the whole population reached statistical significance (p=0.035) while the reduction of bleeding events or subgroup analyses did not.

Due to a higher risk profile in this patient cohort, the rate of thromboembolic events of 3.7% was higher than in other studies that reported events in 1.3 to 3.4% (105, 106, 109, 155-159, 164). The bleeding rate in other studies was similar (4.8%) (105) or lower (0.0-3.4%) (109, 155, 157-159, 164) than in our analysis (5.3%). Other reports confirmed the reduction of events after LAAC compared to historic controls, with a reduction of thromboembolic events of 77-83% (156, 164) and a reduction of bleeding events of 46% (164). The first controlled study that compared LAAC to contemporaneous DOAC therapy proved non-inferiority (110).

Annual mortality in this analysis (8.6%) was similar to other studies (3.7-10.8%) (105, 106, 109, 155-159, 164).

4.3.5 Limitations

While multi-centre real-world registries are valuable tools to monitor the outcome of interventions in daily clinical practice, they face several types of bias and must therefore be interpreted with caution. We tried to eliminate selection bias by including all patients undergoing LAAC in currently active centres in Austria. Reporting bias was minimized by external review at most centres and inclusion of data of the Austrian population registry as well as databases of hospital associations. We therefore achieved a complete follow-up concerning mortality. However, follow-up TOE data was missing in a small proportion of patients. Furthermore, the use of historic controls may generate several types of bias, such as selection bias and time trend effects. This analysis did only include Amplatzer and

Watchman devices. Therefore, this analysis may not be extrapolated to other LAAC devices (sections 2.3.1.1 and 2.3.1.2). Lastly, the low sample size of individual groups may have led to underestimation of factors which would have a significant impact on outcome otherwise.

4.3.6 Outlook

The number of annual LAAC implantations is on the rise in Austria, reaching more than 60 procedures in 2018 and 2019. A continuation of the Austrian LAAC registry is ongoing.

5 Conclusion

The main learning points of the aforementioned studies are the following:

- The SAFE-ME study showed that AHRE episodes are very common in pacemaker patients, even in patients with a low atrial pacing rate and without sinus nodal disease. They are not associated with the presence of paroxysmal AF, as someone would expect. This highlights the usefulness of current CIED's arrhythmia detection functions. After the finalization of recruitment and application of the AF initiation algorithm, the study will give important hints about the prediction of AF by Holter ECG.
- The AF-TAVI study found that pre-existing AF has a relevant impact on long-term mortality in TAVI patients. NOAF does not play such a big role in the long run but is associated with increased short-term complications.
- The Austrian LAAC Registry shows that only patients with a high thromboembolic and bleeding risk are selected for LAAC. Bleeding was the most common indication to perform LAAC, but other indications where very heterogeneous, ranging from patient preference to recurrent thromboembolic or bleeding events. A low long-term event rate outweighs the relatively high short-term complication rate in those patients. When compared to historic controls, a reduction of thromboembolic and bleeding events becomes apparent.

6 Summary and perspectives

In this dissertation, various aspects of AF in relation with its prediction and two distinctive cardiac procedures are illuminated. As presented in the introduction, AF represents one of the most important cardiac arrhythmias with severe implications on morbidity and mortality of the general population.

Before focusing on treatment of AF and its consequences, it is crucial to understand that even the diagnosis of AF can be very challenging. A simple Holter ECG may predict patients developing AF with high accuracy in the future, if clinical trials (such as the SAFE-ME study) confirm their notion in the future.

AF and interventional cardiac procedures, such as TAVI, influence each other in two ways. On the one hand, pre-existing AF acts as marker for elevated procedural and post-procedural risk. On the other hand, invasive cardiac procedures lead to changes in cardiac physiology that can trigger the new onset of AF.

Appropriate treatment may become very difficult if the bleeding risk does not allow the use of OAC. An analysis of the Austrian left atrial appendage closure registry gives new hints for adequate patient selection to improve outcome after LAAC.

As the number of cardiac procedures is on the rise (165) and also the prevalence of AF will increase (166), we will have to concentrate on topics associated with AF and cardiac interventions even more in the future.

References

1. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). European heart journal. 2020.

2. Bjorck S, Palaszewski B, Friberg L, Bergfeldt L. Atrial fibrillation, stroke risk, and warfarin therapy revisited: a population-based study. Stroke; a journal of cerebral circulation. 2013;44(11):3103-8.

3. Haim M, Hoshen M, Reges O, Rabi Y, Balicer R, Leibowitz M. Prospective national study of the prevalence, incidence, management and outcome of a large contemporary cohort of patients with incident non-valvular atrial fibrillation. Journal of the American Heart Association. 2015;4(1):e001486.

4. Henriksson KM, Farahmand B, Asberg S, Edvardsson N, Terent A. Comparison of cardiovascular risk factors and survival in patients with ischemic or hemorrhagic stroke. International journal of stroke : official journal of the International Stroke Society. 2012;7(4):276-81.

5. Lang C, Seyfang L, Ferrari J, Gattringer T, Greisenegger S, Willeit K, et al. Do Women With Atrial Fibrillation Experience More Severe Strokes? Results From the Austrian Stroke Unit Registry. Stroke; a journal of cerebral circulation. 2017;48(3):778-80.

6. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263-72.

7. Xiong Q, Proietti M, Senoo K, Lip GY. Asymptomatic versus symptomatic atrial fibrillation: A systematic review of age/gender differences and cardiovascular outcomes. International journal of cardiology. 2015;191:172-7.

8. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al. Subclinical atrial fibrillation and the risk of stroke. The New England journal of medicine. 2012;366(2):120-9.

9. Gorenek BC, Bax J, Boriani G, Chen SA, Dagres N, Glotzer TV, et al. Device-detected subclinical atrial tachyarrhythmias: definition, implications and management-an European Heart Rhythm Association (EHRA) consensus document, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2017;19(9):1556-78.

10. Fox CS, Parise H, D'Agostino RB, Sr., Lloyd-Jones DM, Vasan RS, Wang TJ, et al. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. JAMA : the journal of the American Medical Association. 2004;291(23):2851-5.

11. Ellinor PT, Lunetta KL, Albert CM, Glazer NL, Ritchie MD, Smith AV, et al. Meta-analysis identifies six new susceptibility loci for atrial fibrillation. Nature genetics. 2012;44(6):670-5.

12. Oyen N, Ranthe MF, Carstensen L, Boyd HA, Olesen MS, Olesen SP, et al. Familial aggregation of lone atrial fibrillation in young persons. Journal of the American College of Cardiology. 2012;60(10):917-21.

13. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. Circulation. 1997;96(4):1180-4.

14. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. Lancet. 2009;373(9658):155-66.

15. Schwarzl M, Hamdani N, Seiler S, Alogna A, Manninger M, Reilly S, et al. A porcine model of hypertensive cardiomyopathy: implications for heart failure with preserved ejection fraction. Am J Physiol Heart Circ Physiol. 2015;309(9):H1407-18.

16. Manninger M, Zweiker D, van Hunnik A, Alogna A, Prassl AJ, Schipke J, et al. Arterial hypertension drives arrhythmia progression via specific structural remodeling in a porcine model of atrial fibrillation. Heart rhythm. 2018;15(9):1328-36.

17. Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. Physiological reviews. 2011;91(1):265-325.

18. Christ T, Wettwer E, Voigt N, Hala O, Radicke S, Matschke K, et al. Pathology-specific effects of the IKur/Ito/IK,ACh blocker AVE0118 on ion channels in human chronic atrial fibrillation. British journal of pharmacology. 2008;154(8):1619-30.

19. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation. 1995;92(7):1954-68.

20. Davis PH, Dambrosia JM, Schoenberg BS, Schoenberg DG, Pritchard DA, Lilienfeld AM, et al. Risk factors for ischemic stroke: a prospective study in Rochester, Minnesota. Annals of neurology. 1987;22(3):319-27.

21. Versteeg HH, Heemskerk JWM, Levi M, Reitsma PH. New Fundamentals in Hemostasis. Physiological reviews. 2013;93(1):327-58.

22. Darlington A, McCauley MD. Atrial Cardiomyopathy: An Unexplored Limb of Virchow's Triad for AF Stroke Prophylaxis. Front Cardiovasc Med. 2020;7:11.

23. Glikson M, Wolff A, Hindricks G, Mandrola J, Camm AJ, Lip G, et al. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion – an update. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2019;15(13):1133-80.

24. Al-Saady NM, Obel OA, Camm AJ. Left atrial appendage: structure, function, and role in thromboembolism. Heart. 1999;82(5):547-54.

25. Madden JL. Resection of the left auricular appendix; a prophylaxis for recurrent arterial emboli. J Am Med Assoc. 1949;140(9):769-72.

26. Transesophageal echocardiographic correlates of thromboembolism in high-risk patients with nonvalvular atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography. Annals of internal medicine. 1998;128(8):639-47.

27. Oneglia C, Rusconi C. Left atrial appendage thrombus as a source of peripheral embolism: TEE evidence of direct relationship. Echocardiography (Mount Kisco, NY). 2001;18(5):389-90.

28. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. The Annals of thoracic surgery. 1996;61(2):755-9.

29. Macfarlane SR, Seatter MJ, Kanke T, Hunter GD, Plevin R. Proteinase-activated receptors. Pharmacological reviews. 2001;53(2):245-82.

30. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on Atrial cardiomyopathies: Definition, characterisation, and clinical implication. Journal of arrhythmia. 2016;32(4):247-78.

31. Hohnloser SH, Capucci A, Fain E, Gold MR, van Gelder IC, Healey J, et al. ASymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and the atrial fibrillation Reduction atrial pacing Trial (ASSERT). American heart journal. 2006;152(3):442-7.

32. Brambatti M, Connolly SJ, Gold MR, Morillo CA, Capucci A, Muto C, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. Circulation. 2014;129(21):2094-9.

33. Han SW, Kim SH, Lee JY, Chu CK, Yang JH, Shin HY, et al. A new subtype classification of ischemic stroke based on treatment and etiologic mechanism. Eur Neurol. 2007;57(2):96-102.

34. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Embolic strokes of undetermined source: the case for a new clinical construct. The Lancet Neurology. 2014;13(4):429-38.

35. Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, et al. Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source. The New England journal of medicine. 2018;378(23):2191-201.

36. Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, et al. Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source. The New England journal of medicine. 2019;380(20):1906-17.

37. Thind M, Holmes DN, Badri M, Pieper KS, Singh A, Blanco RG, et al. Embolic and Other Adverse Outcomes in Symptomatic Versus Asymptomatic Patients With Atrial Fibrillation (from the ORBIT-AF Registry). The American journal of cardiology. 2018;122(10):1677-83.

38. Brandenburg S, Arakel EC, Schwappach B, Lehnart SE. The molecular and functional identities of atrial cardiomyocytes in health and disease. Biochimica et biophysica acta. 2016;1863(7 Pt B):1882-93.

39. Rahimtoola SH, Ehsani A, Sinno MZ, Loeb HS, Rosen KM, Gunnar RM. Left atrial transport function in myocardial infarction. Importance of its booster pump function. The American journal of medicine. 1975;59(5):686-94.

40. Umana E, Solares CA, Alpert MA. Tachycardia-induced cardiomyopathy. The American journal of medicine. 2003;114(1):51-5.

41. Gossage AM, Hicks JAB. On auricular fibrillation. Q J Med. 1913;6(24):435-40.

42. Zweiker D, Bisping E, Lercher P, Manninger M, Prenner G, Riedlbauer R, et al. Incessant WPW syndrome. [German]. Journal fur Kardiologie. 2018;25(5-6):148-9.

43. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ, Swedberg KB, et al. Predictors of mortality and morbidity in patients with chronic heart failure. European heart journal. 2006;27(1):65-75.

44. Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. The Lancet. 2010;376(9744):886-94.

45. Guo Y, Lane DA, Wang L, Zhang H, Wang H, Zhang W, et al. Mobile Health Technology to Improve Care for Patients With Atrial Fibrillation. Journal of the American College of Cardiology. 2020;75(13):1523-34.

46. Tan KT, Lip GY. Atrial fibrillation: should we target platelets or the coagulation pathway? Card Electrophysiol Rev. 2003;7(4):370-1.

47. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. The New England journal of medicine. 2011;364(9):806-17.

48. Toohey M. Clinical experience with warfarin sodium. British medical journal. 1958;2(5101):892-3.

49. Harter K, Levine M, Henderson SO. Anticoagulation drug therapy: a review. West J Emerg Med. 2015;16(1):11-7.

50. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2009;361(12):1139-51.

51. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2011;365(11):981-92.

52. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. The New England journal of medicine. 2011;365(10):883-91.

53. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2013;369(22):2093-104.

54. Friberg L, Rosenqvist M, Lip GY. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. Circulation. 2012;125(19):2298-307.

55. Kotecha D. RATE-AF: Rate control therapy evaluation in permanent atrial fibrillation. ESC Congress 2020 - The Digital Experience: European Society of Cardiology; 2020. p. 12.

56. Pluymaekers N, Dudink E, Luermans J, Meeder JG, Lenderink T, Widdershoven J, et al. Early or Delayed Cardioversion in Recent-Onset Atrial Fibrillation. The New England journal of medicine. 2019;380(16):1499-508.

57. Airaksinen KE, Gronberg T, Nuotio I, Nikkinen M, Ylitalo A, Biancari F, et al. Thromboembolic complications after cardioversion of acute atrial fibrillation: the FinCV (Finnish CardioVersion) study. Journal of the American College of Cardiology. 2013;62(13):1187-92.

58. Cox JL, Schuessler RB, D'Agostino HJ, Jr., Stone CM, Chang BC, Cain ME, et al. The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. The Journal of thoracic and cardiovascular surgery. 1991;101(4):569-83.

59. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous Initiation of Atrial Fibrillation by Ectopic Beats Originating in the Pulmonary Veins. New England Journal of Medicine. 1998;339(10):659-66.

60. Calkins H, Hindricks G, Cappato R, Kim Y-H, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart rhythm. 2017;14(10):e275-e444.

61. Hindricks G, Piorkowski C, Tanner H, Kobza R, Gerds-Li JH, Carbucicchio C, et al. Perception of atrial fibrillation before and after radiofrequency catheter ablation: relevance of asymptomatic arrhythmia recurrence. Circulation. 2005;112(3):307-13.

62. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al. Catheter Ablation for Atrial Fibrillation with Heart Failure. The New England journal of medicine. 2018;378(5):417-27.

63. Rienstra M, Hobbelt AH, Alings M, Tijssen JGP, Smit MD, Brügemann J, et al. Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial. European heart journal. 2018;39(32):2987-96.

64. Wakula P, Neumann B, Kienemund J, Thon-Gutschi E, Stojakovic T, Manninger M, et al. CHA2DS2-VASc score and blood biomarkers to identify patients with atrial high-rate

episodes and paroxysmal atrial fibrillation. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2017;19(4):544-51.

65. Bonizzi P, Zeemering S, Karel JM, Di Marco LY, Uldry L, Van Zaen J, et al. Systematic comparison of non-invasive measures for the assessment of atrial fibrillation complexity: a step forward towards standardization of atrial fibrillation electrogram analysis. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2015;17(2):318-25.

66. Brugada J, Katritsis DG, Arbelo E, Arribas F, Bax JJ, Blomström-Lundqvist C, et al. 2019 ESC Guidelines for the management of patients with supraventricular tachycardiaThe Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). European heart journal. 2019;41(5):655-720.

67. Guo Y, Wang H, Zhang H, Liu T, Liang Z, Xia Y, et al. Mobile Health Technology for Atrial Fibrillation Screening Using Photoplethysmography-Based Smart Devices: The HUAWEI Heart study. Journal of the American College of Cardiology. 2019;74(19):2365-75.

68. Kwon S, Hong J, Choi EK, Yi Y, Jeong ER, Byunghwan L, et al. A novel ring-type wearable device equipped with deep learning algorithm using photoplethysmographic signals for detecting atrial fibrillation. Heart rhythm. 2019;16(5):S631.

69. Botto GL, Padeletti L, Santini M, Capucci A, Gulizia M, Zolezzi F, et al. Presence and duration of atrial fibrillation detected by continuous monitoring: crucial implications for the risk of thromboembolic events. Journal of cardiovascular electrophysiology. 2009;20(3):241-8.

70. Magnani JW, Rienstra M, Lin H, Sinner MF, Lubitz SA, McManus DD, et al. Atrial fibrillation: current knowledge and future directions in epidemiology and genomics. Circulation. 2011;124(18):1982-93.

71. Rienstra M, McManus DD, Benjamin EJ. Novel risk factors for atrial fibrillation: useful for risk prediction and clinical decision making? Circulation. 2012;125(20):e941-6.

72. Stafford PJ, Kolvekar S, Cooper J, Fothergill J, Schlindwein F, deBono DP, et al. Signal averaged P wave compared with standard electrocardiography or echocardiography for prediction of atrial fibrillation after coronary bypass grafting. Heart. 1997;77(5):417-22.

73. Perez MV, Dewey FE, Marcus R, Ashley EA, Al-Ahmad AA, Wang PJ, et al. Electrocardiographic predictors of atrial fibrillation. American heart journal. 2009;158(4):622-8.

74. Cabasson A, Dang L, Vésin J-M, Buttu A, Abächerli R, Leber R, et al. P-wave indices to detect susceptibility to atrial fibrillation. Computing in Cardiology. 2011;38:257-60.

75. Vassilikos V, Dakos G, Chatzizisis YS, Chouvarda I, Karvounis C, Maynard C, et al. Novel non-invasive P wave analysis for the prediction of paroxysmal atrial fibrillation recurrences in patients without structural heart disease: a prospective pilot study. International journal of cardiology. 2011;153(2):165-72.

76. Salah A, Zhou S, Liu Q, Yan H. P wave indices to predict atrial fibrillation recurrences post pulmonary vein isolation. Arquivos brasileiros de cardiologia. 2013;101(6):519-27.

77. Martinez A, Alcaraz R, Rieta JJ. Gaussian modeling of the P-wave morphology time course applied to anticipate paroxysmal atrial fibrillation. Computer methods in biomechanics and biomedical engineering. 2015;18(16):1775-84.

78. Alexander B, Milden J, Hazim B, Haseeb S, Bayes-Genis A, Elosua R, et al. New electrocardiographic score for the prediction of atrial fibrillation: The MVP ECG risk score (morphology-voltage-P-wave duration). Ann Noninvasive Electrocardiol. 2019;24(6):e12669.

79. Nakatani Y, Sakamoto T, Yamaguchi Y, Tsujino Y, Kataoka N, Kinugawa K. Coefficient of variation of P-wave duration measured using an automated measurement system predicts recurrence of atrial fibrillation. Journal of electrocardiology. 2019;53:79-84.

80. Hayn D, Kollmann A, Schreier G. Predicting initiation and termination of atrial fibrillation from the ECG. Biomedizinische Technik Biomedical engineering. 2007;52(1):5-10.

81. Hayn D. Development, Validation, and Optimisation of High-Quality ECG Processing Algorithms. Hall/Tirol: University for Health Sciences, Medical Informatics and Technology; 2007.

82. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. European heart journal. 2017;38(36):2739-91.

83. Osnabrugge RL, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. Journal of the American College of Cardiology. 2013;62(11):1002-12.

84. Généreux P, Stone GW, O'Gara PT, Marquis-Gravel G, Redfors B, Giustino G, et al. Natural History, Diagnostic Approaches, and Therapeutic Strategies for Patients With Asymptomatic Severe Aortic Stenosis. Journal of the American College of Cardiology. 2016;67(19):2263-88.

85. Carabello BA, Paulus WJ. Aortic stenosis. Lancet. 2009;373(9667):956-66.

86. Mordi I, Tzemos N. Bicuspid aortic valve disease: a comprehensive review. Cardiol Res Pract. 2012;2012:196037-.

87. Ramanathan T, Skinner H. Coronary blood flow. Continuing Education in Anaesthesia Critical Care & Pain. 2005;5(2):61-4.

88. Messika-Zeitoun D, Lloyd G. Aortic valve stenosis: evaluation and management of patients with discordant grading. e-Journal of Cardiology Practice. 2018;15(26):1.

89. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation. 2002;106(24):3006-8.

90. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. The New England journal of medicine. 2019;380(18):1695-705.

91. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. The New England journal of medicine. 2014;370(19):1790-8.

92. Eggebrecht H, Mehta RH. Transcatheter aortic valve implantation (TAVI) in Germany: more than 100,000 procedures and now the standard of care for the elderly. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2019;14(15):e1549-e52.

93. Chopard R, Teiger E, Meneveau N, Chocron S, Gilard M, Laskar M, et al. Baseline Characteristics and Prognostic Implications of Pre-Existing and New-Onset Atrial Fibrillation After Transcatheter Aortic Valve Implantation: Results From the FRANCE-2 Registry. JACC Cardiovasc Interv. 2015;8(10):1346-55.

94. Kotting J, Schiller W, Beckmann A, Schafer E, Dobler K, Hamm C, et al. German Aortic Valve Score: a new scoring system for prediction of mortality related to aortic valve

procedures in adults. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2013;43(5):971-7.

95. Zhang H, El-Am EA, Thaden JJ, Pislaru SV, Scott CG, Krittanawong C, et al. Atrial fibrillation is not an independent predictor of outcome in patients with aortic stenosis. Heart. 2019;106(4):280-6.

96. Jorgensen TH, Thygesen JB, Thyregod HG, Svendsen JH, Sondergaard L. New-onset atrial fibrillation after surgical aortic valve replacement and transcatheter aortic valve implantation: a concise review. The Journal of invasive cardiology. 2015;27(1):41-7.

97. Lopez-Marco A, Miller H, Youhana A, Ashraf S, Zaidi A, Bhatti F, et al. Low-flow low-gradient aortic stenosis: surgical outcomes and mid-term results after isolated aortic valve replacement. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2016;49(6):1685-90.

98. Villablanca PA, Mathew V, Thourani VH, Rodes-Cabau J, Bangalore S, Makkiya M, et al. A meta-analysis and meta-regression of long-term outcomes of transcatheter versus surgical aortic valve replacement for severe aortic stenosis. International journal of cardiology. 2016;225:234-43.

99. Girerd N, Magne J, Pibarot P, Voisine P, Dagenais F, Mathieu P. Postoperative atrial fibrillation predicts long-term survival after aortic-valve surgery but not after mitral-valve surgery: a retrospective study. BMJ open. 2011;1(2):e000385.

100. Alexander B, Rodriguez C, de la Isla LP, Islas F, Quevedo PJ, Nombela-Franco L, et al. The impact of advanced Interatrial block on new-onset atrial fibrillation following TAVR procedure. International journal of cardiology. 2016;223:672-3.

101. Sievert H, Lesh MD, Trepels T, Omran H, Bartorelli A, Della Bella P, et al. Percutaneous left atrial appendage transcatheter occlusion to prevent stroke in high-risk patients with atrial fibrillation: early clinical experience. Circulation. 2002;105(16):1887-9.

102. Sanchez CE, Yakubov SJ, Amin A, Arshi A. Left Atrial Appendage Closure: Technical Considerations of Endocardial Closure. Cardiac electrophysiology clinics. 2020;12(1):47-54.

103. Koneru JN, Badhwar N, Ellenbogen KA, Lee RJ. LAA ligation using the LARIAT suture delivery device: tips and tricks for a successful procedure. Heart rhythm. 2014;11(5):911-21.

104. Freixa X, Martin-Yuste V. Percutaneous left atrial appendage occlusion. Revista espanola de cardiologia (English ed). 2013;66(12):919-22.

105. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet. 2009;374(9689):534-42.

106. Holmes DR, Jr., Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. Journal of the American College of Cardiology. 2014;64(1):1-12.

107. Glikson M, Wolff R, Hindricks G, Mandrola J, Camm AJ, Lip GYH, et al. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion - an update. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2020;22(2):184a-av.

108. Boersma LV, Schmidt B, Betts TR, Sievert H, Tamburino C, Teiger E, et al. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. European heart journal. 2016;37(31):2465-74.

109. Tzikas A, Shakir S, Gafoor S, Omran H, Berti S, Santoro G, et al. Left atrial appendage occlusion for stroke prevention in atrial fibrillation: multicentre experience with the AMPLATZER Cardiac Plug. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2016;11(10):1170-9.

110. Osmancik P, Herman D, Neuzil P, Hala P, Taborsky M, Kala P, et al. Left Atrial Appendage Closure Versus Direct Oral Anticoagulants in High-Risk Patients With Atrial Fibrillation. Journal of the American College of Cardiology. 2020;75(25):3122-35.

111. Filos D, Tachmatzidis D, Maglaveras N, Vassilikos V, Chouvarda I. Understanding the Beat-to-Beat Variations of P-Waves Morphologies in AF Patients During Sinus Rhythm: A Scoping Review of the Atrial Simulation Studies. Frontiers in physiology. 2019;10:742-.

112. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. BMC Med Res Methodol. 2010;10:1.

113. Zweiker D, Froschl M, Tiede S, Weidinger P, Schmid J, Manninger M, et al. Atrial fibrillation in transcatheter aortic valve implantation patients: Incidence, outcome and predictors of new onset. Journal of electrocardiology. 2017;50(4):402-9.

114. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. European heart journal. 2012;33(19):2403-18.

115. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2012;41(4):734-44; discussion 44-5.

116. Zweiker D, Sieghartseitner R, Fiedler L, Toth-Gayor G, Luha O, Stix G, et al. Indications and Outcome in Patients Undergoing Left Atrial Appendage Closure—The Austrian LAAC Registry. Journal of Clinical Medicine. 2020;9(10):3274.

117. Meier B, Blaauw Y, Khattab AA, Lewalter T, Sievert H, Tondo C, et al. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2015;10(9):1109-25.

118. Lebhart G, Neustädter C, Kytir J. The new Population Register at Statistics Austria: Conceptualization and Methodology for Register-based Flow and Stock Statistics. Austrian Journal of Statistics. 2007;36(4):277-89.

119. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. Bmj. 2011;342:d124.

120. Olesen JB, Lip GY, Hansen PR, Lindhardsen J, Ahlehoff O, Andersson C, et al. Bleeding risk in 'real world' patients with atrial fibrillation: comparison of two established bleeding prediction schemes in a nationwide cohort. J Thromb Haemost. 2011;9(8):1460-7.

121. LaHaye SA, Gibbens SL, Ball DG, Day AG, Olesen JB, Skanes AC. A clinical decision aid for the selection of antithrombotic therapy for the prevention of stroke due to atrial fibrillation. European heart journal. 2012;33(17):2163-71.

122. Ziegler PD, Glotzer TV, Daoud EG, Singer DE, Ezekowitz MD, Hoyt RH, et al. Detection of previously undiagnosed atrial fibrillation in patients with stroke risk factors and usefulness of continuous monitoring in primary stroke prevention. The American journal of cardiology. 2012;110(9):1309-14.

123. Ziegler PD, Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, et al. Incidence of newly detected atrial arrhythmias via implantable devices in patients with a

history of thromboembolic events. Stroke; a journal of cerebral circulation. 2010;41(2):256-60.

124. Gillis AM, Morck M. Atrial fibrillation after DDDR pacemaker implantation. Journal of cardiovascular electrophysiology. 2002;13(6):542-7.

125. Glotzer TV, Hellkamp AS, Zimmerman J, Sweeney MO, Yee R, Marinchak R, et al. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MOde Selection Trial (MOST). Circulation. 2003;107(12):1614-9.

126. Kezerashvili A, Krumerman AK, Fisher JD. Sinus Node Dysfunction in Atrial Fibrillation: Cause or Effect? Journal of atrial fibrillation. 2008;1(3):30-.

127. Pollak WM, Simmons JD, Interian A, Jr., Atapattu SA, Castellanos A, Myerburg RJ, et al. Clinical utility of intraatrial pacemaker stored electrograms to diagnose atrial fibrillation and flutter. Pacing and clinical electrophysiology : PACE. 2001;24(4 Pt 1):424-9.

128. Kirchhof P, Blank BF, Calvert M, Camm AJ, Chlouverakis G, Diener HC, et al. Probing oral anticoagulation in patients with atrial high rate episodes: Rationale and design of the Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes (NOAH-AFNET 6) trial. American heart journal. 2017;190:12-8.

129. Lopes RD, Alings M, Connolly SJ, Beresh H, Granger CB, Mazuecos JB, et al. Rationale and design of the Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA) trial. American heart journal. 2017;189:137-45.

130. Walther T, Hamm CW, Schuler G, Berkowitsch A, Kotting J, Mangner N, et al. Perioperative Results and Complications in 15,964 Transcatheter Aortic Valve

Replacements: Prospective Data From the GARY Registry. Journal of the American College of Cardiology. 2015;65(20):2173-80.

131. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. European heart journal. 2006;27(8):949-53.

132. Urena M, Hayek S, Cheema AN, Serra V, Amat-Santos IJ, Nombela-Franco L, et al. Arrhythmia burden in elderly patients with severe aortic stenosis as determined by continuous electrocardiographic recording: toward a better understanding of arrhythmic events after transcatheter aortic valve replacement. Circulation. 2015;131(5):469-77.

133. Sannino A, Gargiulo G, Schiattarella GG, Perrino C, Stabile E, Losi MA, et al. A meta-analysis of the impact of pre-existing and new-onset atrial fibrillation on clinical outcomes in patients undergoing transcatheter aortic valve implantation. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2016;12(8):e1047-e56.

134. Arsalan M, Maren W, Hecker F, Filardo G, Kim WK, Pollock BD, et al. TAVI risk scoring using established versus new scoring systems: role of the new STS/ACC model. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2018;13(13):1520-6.

135. Joint Task Force on the Management of Valvular Heart Disease of the European Society of C, European Association for Cardio-Thoracic S, Vahanian A, Alfieri O, Andreotti F, Antunes MJ, et al. Guidelines on the management of valvular heart disease (version 2012). European heart journal. 2012;33(19):2451-96.

136. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease:

a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(23):e521-643.

137. Iung B, Laouenan C, Himbert D, Eltchaninoff H, Chevreul K, Donzeau-Gouge P, et al. Predictive factors of early mortality after transcatheter aortic valve implantation: individual risk assessment using a simple score. Heart. 2014;100(13):1016-23.

138. Seiffert M, Sinning JM, Meyer A, Wilde S, Conradi L, Vasa-Nicotera M, et al. Development of a risk score for outcome after transcatheter aortic valve implantation. Clinical research in cardiology : official journal of the German Cardiac Society. 2014;103(8):631-40.

139. Edwards FH, Cohen DJ, O'Brien SM, Peterson ED, Mack MJ, Shahian DM, et al. Development and Validation of a Risk Prediction Model for In-Hospital Mortality After Transcatheter Aortic Valve Replacement. JAMA cardiology. 2016;1(1):46-52.

140. Biviano AB, Nazif T, Dizon J, Garan H, Fleitman J, Hassan D, et al. Atrial Fibrillation Is Associated With Increased Mortality in Patients Undergoing Transcatheter Aortic Valve Replacement: Insights From the Placement of Aortic Transcatheter Valve (PARTNER) Trial. Circulation Cardiovascular interventions. 2016;9(1):e002766.

141. Shaul AA, Kornowski R, Bental T, Vaknin-Assa H, Assali A, Golovchiner G, et al. Type of Atrial Fibrillation and Clinical Outcomes in Patients Undergoing Transcatheter Aortic Valve Replacement. Ann Noninvasive Electrocardiol. 2016;21(5):519-25.

142. Siontis GCM, Praz F, Lanz J, Vollenbroich R, Roten L, Stortecky S, et al. New-onset arrhythmias following transcatheter aortic valve implantation: a systematic review and meta-analysis. Heart. 2018;104(14):1208-15.

143. Tanawuttiwat T, O'Neill BP, Cohen MG, Chinthakanan O, Heldman AW, Martinez CA, et al. New-onset atrial fibrillation after aortic valve replacement: comparison of

transfemoral, transapical, transaortic, and surgical approaches. Journal of the American College of Cardiology. 2014;63(15):1510-9.

144. Auer J, Weber T, Berent R, Ng CK, Lamm G, Eber B. Risk factors of postoperative atrial fibrillation after cardiac surgery. Journal of cardiac surgery. 2005;20(5):425-31.

145. Amat-Santos IJ, Rodes-Cabau J, Urena M, DeLarochelliere R, Doyle D, Bagur R, et al. Incidence, predictive factors, and prognostic value of new-onset atrial fibrillation following transcatheter aortic valve implantation. Journal of the American College of Cardiology. 2012;59(2):178-88.

146. Nuis RJ, Van Mieghem NM, Schultz CJ, Moelker A, van der Boon RM, van Geuns RJ, et al. Frequency and causes of stroke during or after transcatheter aortic valve implantation. The American journal of cardiology. 2012;109(11):1637-43.

147. Asmarats L, Nault I, Ferreira-Neto AN, Muntané-Carol G, Del Val D, Junquera L, et al. Prolonged Continuous Electrocardiographic Monitoring Prior to Transcatheter Aortic Valve Replacement: The PARE Study. JACC Cardiovasc Interv. 2020;13(15):1763-73.

148. Schmid J, Stojakovic T, Zweiker D, Scharnagl H, Maderthaner RD, Scherr D, et al. ST2 predicts survival in patients undergoing transcatheter aortic valve implantation. International journal of cardiology. 2017;244:87-92.

149. Barbieri F, Senoner T, Adukauskaite A, Dobner S, Holfeld J, Semsroth S, et al. Long-Term Prognostic Value of High-Sensitivity Troponin T Added to N-Terminal Pro Brain Natriuretic Peptide Plasma Levels Before Valve Replacement for Severe Aortic Stenosis. The American journal of cardiology. 2019;124(12):1932-9.

150. Pagnesi M, Kim WK, Conradi L, Barbanti M, Stefanini GG, Zeus T, et al. Transcatheter Aortic Valve Replacement With Next-Generation Self-Expanding Devices: A Multicenter, Retrospective, Propensity-Matched Comparison of Evolut PRO Versus Acurate neo Transcatheter Heart Valves. JACC Cardiovasc Interv. 2019;12(5):433-43.

151. Pagnesi M, Kim WK, Conradi L, Barbanti M, Stefanini GG, Schofer J, et al. Impact of Predilatation Prior to Transcatheter Aortic Valve Implantation With the Self-Expanding Acurate neo Device (from the Multicenter NEOPRO Registry). The American journal of cardiology. 2020;125(9):1369-77.

152. Zweiker D, Maier R, Lamm G, Maurer E, Heigert M, Neunteufl T, et al. The Austrian transcatheter aortic valve implantation (TAVI) Registry--3 years' data. International journal of cardiology. 2014;177(1):114-6.

153. Egger F, Zweiker D, Freynhofer MK, Loffler V, Rohla M, Geppert A, et al. Impact of On-Site Cardiac Surgery on Clinical Outcomes After Transfemoral Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv. 2018;11(21):2160-7.

154. Hutt E, Wazni OM, Kaur S, Saliba WI, Tarakji KG, Kapadia S, et al. Left Atrial Appendage Closure Device Implantation in Patients at Very High Risk for Stroke. Heart rhythm. 2019;17(1):27-32.

155. Urena M, Rodes-Cabau J, Freixa X, Saw J, Webb JG, Freeman M, et al. Percutaneous left atrial appendage closure with the AMPLATZER cardiac plug device in patients with nonvalvular atrial fibrillation and contraindications to anticoagulation therapy. Journal of the American College of Cardiology. 2013;62(2):96-102.

156. Reddy VY, Mobius-Winkler S, Miller MA, Neuzil P, Schuler G, Wiebe J, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). Journal of the American College of Cardiology. 2013;61(25):2551-6.

157. Kefer J, Vermeersch P, Budts W, Depotter T, Aminian A, Benit E, et al. Transcatheter left atrial appendage closure for stroke prevention in atrial fibrillation with Amplatzer cardiac plug: the Belgian Registry. Acta cardiologica. 2013;68(6):551-8.

158. Lopez-Minguez JR, Nogales-Asensio JM, Infante De Oliveira E, De Gama Ribeiro V, Ruiz-Salmeron R, Arzamendi-Aizpurua D, et al. Long-term Event Reduction After Left Atrial Appendage Closure. Results of the Iberian Registry II. Revista espanola de cardiologia (English ed). 2019;72(6):449-55.

159. Santoro G, Meucci F, Stolcova M, Rezzaghi M, Mori F, Palmieri C, et al. Percutaneous left atrial appendage occlusion in patients with non-valvular atrial fibrillation: implantation and up to four years follow-up of the AMPLATZER Cardiac Plug. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2016;11(10):1188-94.

160. Landmesser U, Tondo C, Camm J, Diener HC, Paul V, Schmidt B, et al. Left atrial appendage occlusion with the AMPLATZER Amulet device: one-year follow-up from the prospective global Amulet observational registry. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2018;14(5):e590-e7.

161. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. Circulation. 2011;123(4):417-24.

162. Fastner C, Nienaber CA, Park JW, Brachmann J, Zeymer U, Goedde M, et al. Impact of left atrial appendage morphology on indication and procedural outcome after interventional occlusion: results from the prospective multicentre German LAARGE registry. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2018;14(2):151-7.

163. Freixa X, Cruz-Gonzalez I, Regueiro A, Nombela-Franco L, Estevez-Loureiro R, Ruiz-Salmeron R, et al. Left Atrial Appendage Occlusion as Adjunctive Therapy to

Anticoagulation for Stroke Recurrence. The Journal of invasive cardiology. 2019;31(8):212-6.

164. Boersma LV, Ince H, Kische S, Pokushalov E, Schmitz T, Schmidt B, et al. Evaluating Real-World Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology. Circulation Arrhythmia and electrophysiology. 2019;12(4):e006841.

165. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). European heart journal. 2013;34(29):2281-329.

166. Krijthe BP, Kunst A, Benjamin EJ, Lip GYH, Franco OH, Hofman A, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. European heart journal. 2013;34(35):2746-51.

Appendix

Publications originating from the doctoral study

All mentioned publications were created during the doctoral study.

Main papers

Zweiker, D; Sieghartsleitner, R; Fiedler, L; Toth-Gayor G; Luha, O; Stix, G; Gabriel, H; Vock, P; Lileg, B; Strouhal, A; Delle-Karth, G; Pfeffer, M; Aichinger, J; Tkalec, W; Steinwender, C; Sihorsch, K; Binder, RK; Rammer, M; Barbieri, F; Mueller, S; Verheyen, N; Ablasser, K; Zirlik, A; Scherr, D. Indications and Outcome in Patients Undergoing Left Atrial Appendage Closure—The Austrian LAAC Registry. *J. Clin. Med.* 2020, *9*, 3274 (**IF 3.303, Top 21-60%)**

Zweiker, D; Fröschl, M; Tiede, S; Weidinger, P; Schmid, J; Manninger, M; Brussee, H; Zweiker, R; Binder, J; Mächler, H; Marte, W; Maier, R; Luha, O; Schmidt, A; Scherr, D. Atrial fibrillation in transcatheter aortic valve implantation patients: Incidence, outcome and predictors of new onset. J Electrocardiol. 2017; 50(4):402-409 (**IF: 1,514**)

Other papers

Pagnesi, M; Won-Keun, K; Conradi, L; Barbanti, M; Stefanini, G G; Schofer, J; Hildick-Smith, D; Pilgrim, T; Abizaid, A; **Zweiker, D**; Testa, L; Taramasso, M; Wolf, A; Webb, JG; Sedaghat, A; Van der Heyden, JAS; Ziviello, F; MacCarthy, P; Hamm, CW; Bhadra, O; Schäfer, U; Costa, G; Tamburino, C; Cannata, F; Reimers, B; Eitan, A; Alsanjari, O; Asami, M; Windecker, S; Siqueira, D; Schmidt, A; Bianchi, G; Bedogni, F; Saccocci, M; Maisano, F; Jensen, CJ; Naber, CK; Alenezi, A; Wood, DA; Sinning, JM; Brouwer, J; Tzalamouras, V; Van Mieghem, NM; Colombo, A; Latib, A. Impact of Predilatation Prior to Transcatheter Aortic Valve Implantation

with the Self-Expanding Acurate neo Device (From the Multicenter NEOPRO Registry). Am J Cardiol. 2020; 125(9): 1369-1377 (**IF 2.843, Top 21-60%**)

Barbieri, F; Senoner, T; Adukauskaite, A; Dobner, S; Holfeld, J; Semsroth, S; Lambert, T; **Zweiker, D**; Theurl, T; Rainer, PP; Schmidt, A; Feuchtner, GM; Steinwender, C; Hoppe, UC; Hintringer, F; Bauer, A; Müller, S; Grimm, M; Pfeifer, BE; Dichtl, W. Long-Term Prognostic Value of High-Sensitivity Troponin T Added to N-Terminal Pro Brain Natriuretic Peptide Plasma Levels Before Valve Replacement for Severe Aortic Stenosis. Am J Cardiol. 2019; 124(12): 1932-1939. (**IF 2.843, Top 21-60%**)

Barbieri, F; Senoner, T; Adukauskaite, A; Dobner, S; Holfeld, J; Semsroth, S; Lambert, T; **Zweiker, D**; Theurl, T; Rainer, PP; Schmidt, A; Feuchtner, GM; Steinwender, C; Hoppe, UC; Hintringer, F; Bauer, A; Müller, S; Grimm, M; Pfeifer, BE; Dichtl, W. Dataset on the prognostic value of cardiac biomarkers used in clinical routine in patients with severe aortic stenosis undergoing valve replacement. Data in Brief. 2020; 29: 105111. (**CiteScore 0.93**)

Pagnesi, M; Won-Keun, K; Conradi, L; Barbanti, M; Stefanini, GG; Zeus, T; Pilgrim, T; Schofer, J; **Zweiker, D**; Testa, L; Taramasso, M; Hildick-Smith, D; Abizaid, A; Wolf, A; Van Mieghem, NM; Sedaghat, A; Wöhrle, J; Khogali, S; Van der Hyden, JAS; Webb, JG; Estévez-Loureiro, R; Mylotte, D; MacCarthy, P; Brugaletta, S; Hamm, CW; Bhadra, O; Schäfer, U; Costa, G; Tamburino, C; Cannata, F; Reimers, B; Veulemans, V; Asami, M; Windecker, S; Eitan, A; Schmidt, A; Bianchi, G; Bedogni, F; Saccoci, M; Maisano, F; Alsanjari, O; Siqueira, D; Jendsen, CJ; Naber, CK; Ziviello, F; Sinning, JM; Seeger, J; Rottbauer, W; Brouwer, J; Alenezi, A; Wood, DA; Tzalamouras, V; Regueiro; A; Colombo, A; Latib, A. Transcatheter aortic valve replacement with next-generation self-expanding devices: a multicenter

propensity-matched comparison of Evolut PRO versus Acurate *neo* transcatheter heart valves. JACC-Cardiovascular Interventions 2019;12(5):433-443 (**IF 8.512, Top 20%**)

Egger, F; **Zweiker D**; Huber, K. Reply: Transfemoral Transcatheter Aortic Valve Replacement and On-Site Cardiac Surgery: More Than a Simple Debate About the Heart Team. JACC-Cardiovascular Interventions 2019;12(3):317-318 (**IF 8.512, Top 20%**)

Egger, F†; **Zweiker, D**†; Freynhofer, MK; Löffler, V; Rohla, M; Geppert, A; Farhan, S; Vogel, B; Falkensammer, J; Kastner, J; Pichler, P; Vock, P; Lamm, G; Luha, O; Schmidt, A; Scherr, D; Hammerer, M; Hoppe, UC; Maurer, E; Grund, M; Lambert, T; Tkalec, W; Sturmberger, T; Zeindlhofer, E; Grabenwöger, M; Huber, K. Impact of on-site cardiac surgery on clinical outcomes after transfemoral transcatheter aortic valve implantation. JACC-Cardiovascular Interventions 2018;11:2160-7; †contributed equally (**IF 8.512, Top 20%**)

Schmid, J; Stojakovic, T; **Zweiker, D**; Scharnagl, H; Maderthaner, RD; Scherr, D; Maier, R; Schmidt, A; März, W; Binder, JS; Rainer, PP. ST2 predicts survival in patients undergoing transcatheter aortic valve implantation. Int J Cardiol. 2017; 244(8):87-92 (**IF: 6,189, Top 20%**)

Abstracts

Zweiker, D; Sieghartseitner, R; Toth, G; Luha, O; Stix, G; Vock, P; Delle-Karth, G; Fiedler, L; Aichinger, J; Steinwender, C; Binder, R. K; Barbieri, F; Ablasser, C; Zirlik, A; Scherr, D. Welcher Fall wird kompliziert? - Prädiktoren für Komplikationen im Österreichischen Herzohrverschlussregister. Clin Res Cardiol 2020; 109(Suppl 1): P1483 [DGK Jahrestagung 2020]

Barbieri, F; Senoner, T; Holfeld, J; Semsroth, S; Lambert, T; **Zweiker, D**; Theurl, T; Rainer, PP; Schmidt, A; Feuchtner, GM; Steinwender, C; Hoppe, U; Mueller, S; Grimm, M; Dichtl, W. High sensitivity troponin t and n-terminal pro brain natriuretic peptide plasma levels predict long-term postoperative survival in patients with severe aortic stenosis admitted for valve implantation. European heart journal 2019; 40 (Supplement 1): 2875. 2019; ESC Congress 2019; [Poster]

Gharibeh; SX; **Zweiker, D**; Binder, J; Toth-Gayor, G; Schmidt, A; Zirlik, A; Zweiker, R. A routine nursing questionnaire adds predictive value to conventional risk scores for TAVI (Transcatheter Aortic Valve Implantation) outcome. European heart journal 2019; 40 (Supplement 1): 2342. 2019; ESC congress 2019 [Poster]

Kamml, C; Schmid, J; **Zweiker, D**; Hatz, D; Zirlik, A; Schmidt, A; Binder, JS; Rainer, P. P579 - Right ventricular functional parameters obtained via cardiac magnetic resonance imaging predict mortality in patients undergoing transcatheter aortic valve implantation (TAVI). Clin Res Cardiol (2019). 2019; 108 (Suppl 2): 1. DGK Herztage; 2019 [Poster]

Barbieri, F; Senoner, T; Adukauskaite, A; Dobner, S; Holfeld, J; Semsroth, S; Lambert, T; **Zweiker, D**; Theurl, T; Peter, R; Schmidt, A; Feuchtner, G; Steinwender, C; Hoppe, UC; Hintringer, F; Muller, S; Grimm, M; Pfeifer, B; Dichtl, W. High sensitivity troponin T and N-terminal pro brain natriuretic peptide plasma levels predict long-term postoperative survival in 3595 patients with severe aortic stenosis admitted for valve implantation: the Tyrolean Aortic Stenosis Study-2 (TASS-2). WIEN KLIN WOCHENSCHR. 2019; 131: 306-307. ÖKG Jahrestagung 2019 [Poster]

Barbieri, F; Senoner, T; Adukauskaite, A; Dobner, S; Holfeld, J; Semsroth, S; Lambert, T; **Zweiker, D**; Theurl, T; Rainer, P; Schmidt, A; Feuchtner, G; Steinwender, C; Hoppe, U; Hintringer, F; Muller, S; Grimm, M; Pfeifer, B; Dichtl, W. Combined biomarker risk stratification with high-sensitivity troponin T and N-terminal pro brain natriuretic peptide in 3595 patients with severe aortic stenosis admitted for valve replacement. WIEN KLIN WOCHENSCHR. 2019; 131: S448-S448. ÖKG Jahrestagung 2019 [Poster]

Zweiker, D; Egger, F; Geppert, A; Rohla, M; Luha, O; Lamm, G; Hammerer, M; Maurer, E; Grund, M; Sturmberger, T; Kastner, J; Zeindlhofer, E; Huber, K. Impact of gender and on-site cardiac surgery on clinical outcomes after transfemoral transcatheter aortic valve replacement. WIEN KLIN WOCHENSCHR. 2019; 131: 324-325. ÖKG Jahrestagung 2019 [Poster]

Zweiker, D; Sieghartsleitner, R; Fiedler, L; Toth, G; Luha, O; Stix, G; Vock, P; Strouhal, A; Schratter, A; Aichinger, J; Sihorsch, K; Binder, RK; Barbieri, F; Scherr, D. Indication and outcome in patients undergoing left atrial appendage closure - Results from the Austrian LAAC Registry. WIEN KLIN WOCHENSCHR. 2019; 131: 270-271. ÖKG Jahrestagung 2019. [Poster]

Pagnesi, M; Won-Keun, K; Conradi, L; Barbanti, M; Stefanini, GG; Zeus, T; Pilgrim, T; Schofer, J; **Zweiker, D**; Testa, L; Taramasso, M; Hildick-Smith, D; Abizaid, A; Wolf, A; Van Mieghem, NM; Sedaghat, A; Wöhrle, J; Khogali, S; Van der Hyden, JAS; Webb, JG; Estévez-Loureiro, R; Mylotte, D; MacCarthy, P; Brugaletta, S; Hamm, CW; Bhadra, O; Schäfer, U; Costa, G; Tamburino, C; Cannata, F; Reimers, B; Veulemans, V; Asami, M; Windecker, S; Eitan, A; Schmidt, A; Bianchi, G; Bedogni, F; Saccoci, M; Maisano, F; Alsanjari, O; Siqueira, D; Jendsen, CJ; Naber, CK; Ziviello, F; Sinning, JM; Seeger, J; Rottbauer, W; Brouwer, J; Alenezi, A; Wood, DA; Tzalamouras, V; Regueiro; A; Colombo, A; Latib, A. Transcatheter aortic valve replacement with next-generation self-expanding devices: a multicenter propensity-matched comparison of Evolut PRO versus Acurate *neo* bioprostheses. TCT 2018; SEP 21-25, 2018; San Diego, CA, UNITED STATES. [Poster]

Zweiker, D; Hatz, D; Schmid, J; Binder, J; Maier, R; Luha, O; Schmidt, A; Scherr, D; Rainer, P. The new STS/ACC TAVI risk score and long-term outcome in TAVI patients. WIEN KLIN WOCHENSCHR. 2018; 130 (Suppl 2): S71. 2018; -ÖKG Jahrestagung; JUN 6-9, 2018; Salzburg, AUSTRIA. [Poster]

Zweiker, D; Hatz, D; Schmid, J; Binder, R; Maier, R; Luha, O; Schmidt, A; Scherr, D; Rainer, P. Invasive vs echocardiographic systolic pulmonary artery pressure for risk assessment in TAVI patients. WIEN KLIN WOCHENSCHR. 2018; 130 (Suppl 2): S16. 2018; -ÖKG Jahrestagung; JUN 6-9, 2018; Salzburg, AUSTRIA. (Featured Poster Session) [Poster]

Zweiker, D; Sieghartsleitner, R; Toth, G; Luha, O; Stix, G; Vock, P; Strouhal, A; Schratter, A; Fiedler, L; Aichinger, J; Sihorsch, K; Binder, RK; Scherr, D. Indications for and outcome in patients undergoing left atrial appendage closure in Austria. WIEN KLIN WOCHENSCHR. 2018; 130 (Suppl 2): S72-73. 2018; -ÖKG Jahrestagung; JUN 6-9, 2018; Salzburg, AUSTRIA. [Poster]

Sieghartsleitner, R; Toth-Gayor, G; **Zweiker, D**; Manninger, M; Odeneg, T; Mastnak, B; Ablasser, K; Verheyen, N; Stoschitzky, G; Maier, R; Luha, O; Brussee, H; Scherr, D. Is there an impact of left

atrial appendage morphology on the incidence of peri device leaks? WIEN KLIN WOCHENSCHR. 2018; 130 (Suppl 2): S118. 2018; -ÖKG Jahrestagung; JUN 6-9, 2018; Salzburg, AUSTRIA. [Poster]

Sieghartsleitner, R; Toth-Gayer, G; **Zweiker, D**; Manninger, M; Odeneg, T; Mastnak, B; Ablasser, K; Stoschitzky, G; Maier, R; Luha, O; Brussee, H; Ebner, J; Scherr, D. Indications for and outcome with the left atrial appendage occluder - A single center experience. J Kardiol 2017; 24(11-12): 297-298. 2017; Kardiologie im Zentrum 2017, OCT 20-31, 2017; Linz, AUSTRIA

Zweiker, D; Sieghartsleitner, R; Toth, G; Luha, O; Stix, G; Vock, P; Delle-Karth, G; Fiedler, L; Aichinger, J; Steinwender, C; Rammer, M; Ablasser, K; Brussee, H; Scherr, D. Indications for and outcome in patients undergoing left atrial appendage closure - Results of the Austrian LAAC Registry. EP Europace, Volume 20, Issue suppl 1, i113. 2018; -EHRA Congress; MAR 18-20, 2018; Barcelona, SPAIN. [Moderated Poster]

Bechtoldt, F; **Zweiker, D**; Scherr, D; Keeling, IM; Puchinger, M; Dapunt, OE. Clinical relevance of p-wave variability in patients receiving transcatheter aortic valve implantation. WIEN KLIN WOCHENSCHR. 2017; 129 (Suppl 1): S30. 2017; -ÖKG Jahrestagung; JUN 7-10, 2017; Salzburg, AUSTRIA. [Poster]

Egger, F; **Zweiker, D**; Geppert, A; Rohla, M; Luha, O; Lamm, G; Hammerer, M; Maurer, E; Grund, M; Sturmberger, T; Zeindlhofer, E; Huber, K. The value of on-site cardiac surgery for patients undergoing transfemoral transcatheter aortic valve implantation. WIEN KLIN WOCHENSCHR. 2017; 129 (Suppl 1): S100. 2017; -ÖKG Jahrestagung; JUN 7-10, 2017; Salzburg, AUSTRIA. [Poster]

Hable, I; Bechtoldt, F; Keeling, IM; **Zweiker, D**; Scherr, D; Puchinger, M; Dapunt, OE. Die P-Wellenvariabilität (PWV) nach TAVI und sutureless Aortenklappen-Implantation. WIEN KLIN WOCHENSCHR. 2017; 129 (Suppl 1): S34. 2017; -ÖKG Jahrestagung; JUN 7-10, 2017; Salzburg, AUSTRIA. [Poster]

Schmid, J; **Zweiker, D**; Stojakovic, T; Scharnagl, H; Maderthaner, R; Scherr, D; Maier, R; Schmidt, A; März, W; Binder, J; Rainer, P. ST2 predicts survival in patients undergoing transcatheter aortic valve implantation. WIEN KLIN WOCHENSCHR. 2017; 129 (Suppl 1): S102. 2017; -ÖKG Jahrestagung; JUN 7-10, 2017; Salzburg, AUSTRIA. [Poster]

Sieghartsleitner, R; Toth-Gayor, G; **Zweiker, D**; Manninger, M; Odeneg, T; Mastnak, B; Ablasser, K; Stoschitzky, G; Maier, R; Luha, O; Brussee, H; Scherr, D. Indications for and outcome with the left atrial appendage occluder - a single center experience. WIEN KLIN WOCHENSCHR. 2017; 129 (Suppl 1): S97. 2017; -ÖKG Jahrestagung; JUN 7-10, 2017; Salzburg, AUSTRIA. [Poster]

Copyright notice

- Figure 1, Figure 2, Figure 5, Figure 6, Figure 8, Figure 9, Figure 10: © David Zweiker 2020. Created with Inkscape 0.92.3 (Inkscape community).
- Figure 3, Figure 4, Figure 7, Figure 11, Figure 12, Figure 13, Figure 14, Figure 15: © David Zweiker 2020. Created with Microsoft Office Professional Plus 2016.
- Figure 16: © David Zweiker 2020. Created with IBM SPSS Statistics 20 (IBM, Armonk, NY)

CRF of the SAFE-ME study

Hereby presented is the current version (V1.0 of 28 November 2018).

Patientenetikett

Datum: _____

Patienten-ID: _____

Telefonnummer: _____

Investigator: _____

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

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