Aus dem

Herz-Zentrum Bodensee Konstanz

Elektrophysiologie

# Comparison of the efficacy and risk of therapy with the vitamin K antagonist Phenprocoumon with new oral anticoagulants in catheter ablation of atrial fibrillation

**Inaugural-Dissertation**
**zur Erlangung des Doktorgrades**
**der Medizin**

**der Medizinischen Fakultät**
**der Eberhard Karls Universität**
**zu Tübingen**

**vorgelegt von**

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**2023**

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Tag der Disputation: 01.06.2023

## Table of Contents

# 1 INTRODUCTION AND EXPLANATION OF THE SCIENTIFIC PROBLEM BEING ADDRESSED

## 1.1 Epidemiology of atrial fibrillation

Atrial fibrillation (AF) is a supraventricular arrhythmia characterized by uncoordinated atrial activation. The regular atrial depolarization and P waves are replaced by fibrillation waves or rapid oscillations that lead to an irregular, mostly tachycardic ventricular response.

Atrial fibrillation is the most common sustained cardiac arrhythmia in Europe and the United States(1). Studies of the last decade show that almost 2,3 million Americans suffer from AF, with an estimated prevalence ranging between 0.5-1 % in the general population(2).

However, the number of hospitalizations and outpatient visits for AF according to European registries indicates an even higher prevalence of AF in Europe. The actual prevalence reported ranges between 1.9-2.9 %, the highest incidence being seen in Germany and Sweden(3).

Despite the two-fold increase in prevalence during the last decade, the asymptomatic nature of the disease leads to an actual underestimation of the real prevalence. An active screening could lead to a better estimation of the prevalence of the AF as well as the economic burden attributed to it.

The progress in technology, especially wearable electrocardiography (ECG) recording technology, is going to address more of this issue. The ongoing Apple Heart Study will provide information on how the pulse irregularity and variability will affect the clinical approach to AF diagnosis(4).

Age is an important factor affecting the prevalence and incidence of AF. AF is present in 0.12%-0.16% of subjects younger than 49 years, 3.7%–4.2% of those aged 60-70 years, and 10%-17% of those aged 80 years or older(3).

AF is more prevalent in men than in women. In the Framingham study, the male  female age-adjusted ratio was 1.7(5)

The studies of the last decade showed a male to female ratio of approximately 1.2:1(6).

AF has been independently associated with significantly increased risk of all-cause mortality, specifically a two-fold increased risk in women and a 1.5-fold increased risk in men(7,8).
The AF-related increased morbidity is mainly attributed to stroke and impaired left ventricular function. An estimate of 20-30% of all strokes is due to AF. Furthermore, a growing number of patients with stroke are diagnosed with 'silent', paroxysmal AF(7,9). Independently of a previous stroke history, AF patients show a higher rate of cognitive decline and vascular dementia. The overall increased morbidity leads to an increase of the hospitalization rate (10-40 %) and ultimately impaired quality of life(7,10).

According to the actual model of increase in AF cases it is estimated that in 2030 the prevalence of AF could be 2.7%–3.3% in the European population of 516-525 million inhabitants, corresponding to 14-17 million AF cases with an incidence of 120,000-215,000 new cases per year. These numbers would correspond to an estimated number of 280,000–340,000 new ischemic strokes, causing 3.5–4 million AF hospitalizations, and 100–120 million outpatient visits. Taken together these numbers reflect the dimension of the upcoming epidemic and the necessity to optimize health care for this increasing patient population(3).

## 1.2 Catheter ablation and atrial fibrillation

Dr. Melvin Scheinman performed in 1981 the first catheter ablation in humans using high-energy direct current (DC) shocks. This was the first step that led to the further development of radiofrequency energy catheters for more precise and successful ablation of cardiac arrhythmias. Arrhythmias attributed to a focal source or an accessory pathway have been successfully treated with an ablation procedure since years.
It was the end of the last century that led to further understanding and developments in catheter ablation technique, making the treatment of more complex rhythms like atrial fibrillation possible.
In 1998, Michelle Haissaguerre and his team located ectopic beats from the pulmonary veins of AF patients and showed their importance in initiating frequent episodes of atrial fibrillation. These triggers responded to treatment with radio-frequency ablation making catheter ablation a new strategy for AF management(11).

With the improvement in technology, catheter ablation has become a well-established option for symptomatic, especially medical therapy refractory patients. The European Society of Cardiology (ESC) Guidelines has recommended it as a reasonable management strategy in patients with symptomatic paroxysmal or persistent AF(12).

There is an ongoing comparison between the risk profile of this invasive treatment procedure and the use of antiarrhythmic agents used in AF management. The recent CASTLE AF study could show a significant reduction of all-cause mortality and the rate of hospitalization in patients with heart failure and reduced ejection fraction, who underwent catheter ablation for AF, compared to patients with antiarrhythmic therapy alone (13).

The last decades have witnessed the evolution of catheter ablation in AF from an experimental procedure status to a routinely performed, standardized therapy. Accordingly, an improvement in technical and operative skills over time reflects on the procedure-related complications rate, making the estimation of the periprocedural complications during this transitional time especially difficult.
This ongoing transition reflected in changing operator and center experience makes the estimation of periprocedural complications rate difficult.
To date, there is a 5-7 % rate of overall complication frequency, among which 2-3% experience life-threatening but mainly treatable complications(8).
The most relevant complications are as listed: stroke/transient ischemic attack (<1%), cardiac tamponade (1–2%), pulmonary vein stenosis (<1%), persistent phrenic nerve palsy (1-2%), and severe oesophageal injury (<0,5%) leading to atrio-oesophageal fistula 7-30 days after ablation(8). The periprocedural death rate has been found to be 0.2-0.46 %(14).

One of the most serious complications of atrial fibrillation ablation are thromboembolic events. The high-risk period for stroke/transient ischemic attack (TIA) begins at the onset of the procedure and peaks in the following 24 hours to 2 weeks after the procedure. The incidence of thromboembolic events ranges from 1% to 6%(15). Clinically silent cerebral emboli (approximately 10%), which can only be documented with cranial magnetic resonance imaging (MRI) and whose clinical significance is currently unclear, have also been reported (16).

These findings make thromboembolic complications, together with the corresponding bleeding and vascular complications, one of the most relevant issues in the management of patients undergoing catheter ablation.

## 1.3 History of oral anticoagulation and mechanisms of action

Since in early 1989, Copenhagen AFASAK was one of the first studies to show the need for anticoagulation in patients with atrial fibrillation to reduce thromboembolic risk (16).

For more than 30 years, it has been contraindicated to use Aspirin as “blood- thinning” therapy for patients with non-valvular atrial fibrillation(16).

The most frequently used vitamin K antagonist (VKA) in Europe is Phenprocoumone (Trade Name Marcumar®), whereas in other countries such as USA Warfarin (Coumadin®) remains the first choice. VKA agents require a tight range of international normalized ratio (INR) between 2.5-3, in order to consider the anticoagulation effective and safe. The real dose-response effect is not well known, since for different patients a different dosage of VKA is required to achieve a therapeutic INR range.

All VKA agents achieve peak plasma concentration in a few hours. However, they differ considerably in their elimination half-life with Warfarin having a half-life of 24-33h whereas Phenprocoumon one of 110-130h(17) long. This could lead to more stable plasma levels. More consistent plasma levels of Phenprocoumon could lead to more stable anticoagulation and, subsequently, a significant reduction in embolic events. Even though VKAs have different pharmacokinetics(17), all novel oral anticoagulants have been compared to Warfarin only (18–24).

Novel oral anticoagulants (NOAC) are used at a fixed dose, due to their predictable dose- response effect. Nevertheless, their mechanisms of action and pharmacodynamics vary between each type of NOAC and there is a notable inter-individual variability depending on the dose intake. Effect variability of pharmacodynamic can depend also on the renal and hepatic function as well as the underlying comorbidities(25).

Apixaban and Rivaroxaban are inhibitors of factor Xa with 8-15h and 9-13h half-life, respectively. Apixaban has an oral bioavailability of 50% compared to Rivaroxaban (80%). For Rivaroxaban 20mg the bioavailability depends on food intake, whereas for

Rivaroxaban in lower doses (15mg and 10mg) there is a higher bioavailability (100%), which is not dependent on food intake(25).
Dabigatran inhibits competitively the activated thrombin factor IIa and the blood clot stability. Dabigatran etexilate is a prodrug, which in order to achieve its bioavailability has to be converted in its active form after being absorbed. Nevertheless, its absorption is not dependent on food intake.  It has a longer half-life of 14-17h(26).

Edoxaban, another factor Xa inhibitor, has a bioavailability of 62% and achieves its steady state concentration after 72h(25).

80% of Dabigatran is excreted from the kidney, whereas Rivaroxaban and Edoxaban take the hepatobiliary route for 50% of the bioavailable form, whereas the other half is excreted from the kidney. Apixaban is only on 1/3 of its form eliminated by the kidney, whereas the other 2/3 is excreted by the biliary and enteric route(25).

## 1.4 Safety and efficacy of oral anticoagulation therapy in patients with non-valvular atrial fibrillation bis Dato

The development of novel oral anticoagulants led to different trials among non-valvular AF patients, comparing their efficacy, in terms of preventing stroke and other thromboembolic events and safety, in terms of bleedings, to Warfarin, a routinely used vitamin K antagonist.

In 2009 the RE-LY study (The Randomized Evaluation of Long-Term Anticoagulation Therapy), a randomized non-inferiority trial, compared the safety and efficacy of Dabigatran 110mg and 150mg, a thrombin antagonist, to INR-adjusted dose Warfarin (INR 2-3) among patients with atrial fibrillation. Dabigatran given at a dose of 110mg was associated with similar rates of stroke and systemic embolism compared to Warfarin (relative risk, RR 0.66), with significantly lower rates of major haemorrhage. Dabigatran at a dose of 150 mg showed lower rates of stroke and systemic embolism but similar rates of major haemorrhage when compared to Warfarin. The RE-LY study shows that the novel oral anticoagulant agent Dabigatran had a more favourable safety profile in terms of major life-threatening bleedings, despite the increase in non-life-threatening gastrointestinal bleedings(27).

The next factor Xa antagonist, Rivaroxaban 20 mg and 15mg daily was also non-inferior compared to Warfarin (INR 2-3) regarding the efficacy on preventing thromboembolic events (hazard ratio, HR 0.76). The Rocket-AF study (The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) showed no significant difference regarding the risk of major bleeding between groups, although intracranial and fatal bleeding occurred less frequently in the Rivaroxaban group(28).

Another Factor Xa antagonist, Apixaban, a direct oral factor Xa inhibitor with rapid absorption, was studied in the randomized, double-blind trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation, ARISTOTLE). In patients with atrial fibrillation, Apixaban 5mg and 2,5mg were superior to Warfarin in preventing stroke or systemic embolism (HR 0.79) and caused less bleeding and lowered mortality(29). The main prevention applied to the haemorrhagic type of stroke.

To put it in other words, oral anticoagulation with Apixaban helped prevent 4 haemorrhagic strokes and 2 ischemic or unknown types of stroke out of 1000 patients. Apixaban at a dose of 5 mg twice daily (or the reduced dose according to the patient characteristics) combined the advantages of reducing the rate of stroke and bleeding compared to Warfarin. Different from the other novel oral anticoagulants, Apixaban was also associated with a reduction of the rates of gastrointestinal bleeding. The reduction of bleeding rates was more favourable for the subgroup of patients with renal impairment(29).

The last oral direct factor Xa Inhibitor, Edoxaban, was studied in a randomized, double-blind, double-dummy trial, ENGAGE AF-TIMI published in 2013. The study outcomes were comparable to the previous agents, showing a non-inferiority to Warfarin with respect to the prevention of stroke or systemic embolism as well as significantly lower rates of bleeding and death from cardiovascular causes(30).

A large number of data were obtained from the insurance companies in Germany regarding anticoagulation therapy in non-valvular atrial fibrillation. Rivaroxaban (15mg and 20mg) was compared with Phenprocoumone (VKA of choice in Germany) in patients with renal impairment between 2012-2016. The use of Rivaroxaban 15mg reduced the risk of the combined endpoint: ischemic stroke and intracranial bleeding (HR 0.78, p=0.05). No superiority for Rivaroxaban could be shown if the endpoints were considered separately as well as when the two given doses of Rivaroxaban were analysed as separate groups(31).

The different patient populations, trial designs, dose regimens and anticoagulation agents with the different pharmacokinetic profile of each agent, make a head-to-head comparison of the NOAC studies exceedingly difficult. The common primary end point is the study of non-inferiority in terms of thromboembolic events as compared to Warfarin. All the above agents have been proven to be non-inferior to Warfarin, mostly due to a reduction in haemorrhagic strokes. A patient cohort with higher stroke risk ($CHA_2DS_2$-VASC score>2) was included in the trials of Endoxaban, Rivaroxaban and Dabigatran 150mg. All NOACs were advantageous compared to Warfarin also when considering the risk of major bleedings(32). The best safety profile belonged to the

reduced Apixaban regime 2,5 mg, twice daily, especially in the elderly population with renal impairment(29).
Despite many real-life data analyses, a randomised head-to-head comparison of novel oral anticoagulant regimes is missing. Because of the huge inhomogeneity of the population groups and lack of exclusion criteria, the results of real-life data are not reliable.

The studies based on real-life data showed no difference between the NOAC agents in terms of efficacy. There was a trend of lower bleeding rates in Apixaban and Dabigatran patients compared to the Rivaroxaban users(27,29).

## 1.5 Use of oral anticoagulation therapy in patients undergoing catheter ablation.

*Comparison of NOAC and VKA in patients undergoing catheter ablation*

Since catheter ablation of atrial fibrillation is broadly accepted usual therapy (8,34), the necessity of evaluating the profile of NOAC as well as defining the best practical use in patients undergoing catheter ablation has increased.

Catheter ablation for atrial fibrillation has been proven to be an efficacious therapy in AF population. Despite the growing popularity of this procedure, there is still a necessity to optimize the periprocedural management in terms of anticoagulation. Since the development of NOAC agents, numerous small trials have tried to address the best practical use of anticoagulation during catheter ablation. With the development of NOAC numerous small trials comparing them with Warfarin were designed and the results of some trials are explained in the following paragraphs (18–22).

Very low rates of cardioembolic events and bleeding complications were observed when comparing Rivaroxaban 20mg to Warfarin in patients undergoing catheter ablation (0% thromboembolic events for Rivaroxaban vs. 8% for Warfarin). The study population had a median $CHA_2DS_2$-VASC score <2 for both groups, which could explain the lower rate of events compared to studies regarding the comparison of the other NOAC to Warfarin(18). Furthermore, the study showed that uninterrupted Rivaroxaban can be used with similar efficacy and safety profile compared to VKA in catheter ablation of atrial fibrillation(18,19).

A non-inferiority, in terms of cardioembolic complications and bleedings after catheter ablation of atrial fibrillation has been proved also for Apixaban (5mg and 2,5mg according the dose intake criteria) compared to Warfarin. Silent cerebral infarctions diagnosed with magnetic resonance imaging were also included in the stroke definition(20).

The same can be said for the use of uninterrupted Edoxaban (60mg and 30mg) in patients undergoing catheter ablation of atrial fibrillation compared to VKA, although this study combined a composite endpoint of bleedings and cardioembolic complications(21).

Uninterrupted Dabigatran therapy in patients undergoing catheter ablation for AF was associated with similar thromboembolic events and generally lower bleedings compared to Warfarin(22,23). On the other hand the interruption of Dabigatran and bridging with low molecular-weight Heparin (LMWH) seemed to increase both the risk of thromboembolic and bleeding events on patients undergoing catheter ablation(24).

*Focus on interruption practice and bridging with Heparin*

In the above-mentioned studies Rivaroxaban was paused on the morning of catheter ablation and taken up to 6 hours after haemostasis(18), whereas the morning doses of Apixaban and Dabigatran prior to catheter ablation was skipped (20,22,23). Regardless of NOAC interruption before the procedure, intraprocedural use of unfractionated Heparin was given (UFH) with an active clotting time (ACT) target of at least >300s)

Higher intraprocedural UFH doses were necessary in the patients anticoagulated with Apixaban and Rivaroxaban as compared to the ones on Warfarin(18–20). For Dabigatran, the ACT achieved was higher for the group without bleedings compared to the group with bleeding complications, without a significant impact on embolic events. According to the authors this paradoxical finding was attributed to the bridging therapy with LMWH(24).

The fact that more intraprocedural Heparin is necessary to achieve target ACT for uninterrupted NOAC compared to uninterrupted VKA rise further doubts on the reliability of ACT measurements in patients under NOAC therapy (35).

Catheter ablation procedure has a relevant bleeding risk, mostly in the form of pericardial tamponade. Because of this possible life-threatening complication, for many years it was advised and general practice to pause the VKA prior to the procedure and re-start it after catheter ablation. When interrupted, VKA was often bridged with LMWH(36). Observational studies of the last decade, showed that

bridging therapy was not safe. On the contrary, both the risk of bleeding and cardioembolic events could be reduced when performing an ablation on uninterrupted VKA(37) therapy.

*Recommendations regarding the interruption of oral anticoagulation and other general information*

The recommendations for the use of NOAC during catheter ablation procedure remain still unclear. There is a higher risk for both embolic events and bleeding when NOAC are bridged. As a consequence bridging of NOAC is not recommended. (36,38). A recent practical guideline from 2018 for the use of NOAC categorise catheter ablation as a procedure with low bleeding risk and suggests an interruption of at least 24 hours for all NOAC(38). Whether the rate of thromboembolic events changes when NOAC is not interrupted on the day of catheter ablation remains unknown.

Regarding to the German ´Fachinformation´ only Dabigatran can be uninterruptedly used in patients undergoing catheter ablation for AF whereas for Rivaroxaban and Apixaban an interruption of at least 24h is recommended.

The latest suggestion from the European Society of Cardiology is that oral anticoagulation should not be interrupted at all before performing a catheter ablation(34).

Furthermore, all studies comparing uninterrupted NOAC to Warfarin therapy during catheter ablation procedure of atrial fibrillation have numerous study limitations such as: small population group, different bleeding definitions, composite end points etc. Thus, applying these results in the everyday clinical life is complicated (18–24).

In October 2015, an antidote for Dabigatran, Idarucizumab was approved. Andexanet alpha, the antidote for factor Xa inhibitors Rivaroxaban and Apixaban, was approved 4 years later.

A head to head comparison of Rivaroxaban 15mg and Dabigatran 110mg on catheter ablation for atrial fibrillation suggests a higher thrombotic risk for the Rivaroxaban(40)

group. Other studies that directly compare the impact of factor X antagonist to thrombin inhibitors are missing.

Most of the observational multicentre studies for NOACs with not very well controlled data collection and volunteering participation, do not always reflect the clinical reality(41). On the other hand, in the randomised trials the patient population is being selected for a defined therapy purpose. This process is poorly explained for most studies, which could probably be a selection bias(42). For this reason, monocentric observational studies in consecutive patients could be subject to less practice bias clarifying somehow the reality of every day clinical practice compared to the randomised study situation.

## 1.6 Study outcome of interest

The main purpose of the study is the comparison of efficacy (thromboembolic events) and safety (bleeding complications) of NOAC (Dabigatran, Rivaroxaban and Apixaban) to the vitamin K Antagonist Phenprocoumon among patients undergoing catheter ablation of atrial fibrillation.

The secondary aim is to evaluate if and how other factors such as ablation procedure, duration of the intervention, or interruption of anticoagulation as well as patient characteristics like age, gender or comorbidities, are associated to our primary outcome.

# 2 MATERIAL AND METHODS

## 2.1 Patient population

We studied retrospectively 1735 consecutive patients that underwent 2219 catheter ablation procedures of atrial fibrillation from January 2011 until May 2017 at the Herz-Zentrum Bodensee, Konstanz, Germany (Table 1). Since the aim of our study is to evaluate safety and efficacy of oral anticoagulation specifically in patients undergoing catheter ablation of atrial fibrillation, we consider each ablation procedure as a separate case even if a patient had more than one ablation procedure.
Patients that did not receive an ablation procedure on the left atria such as patients undergoing catheter ablation because of typical flatter or AV-nodal re-entrant tachycardia were excluded. Also, patients taking Edoxaban at the time of catheter ablation were excluded because of the very small number of cases taking Edoxaban (n 21). Patients with a VKA other than Phenprocoumon were also not included in the study.

## 2.2 Catheter ablation procedure and hospitalisation

Patients were hospitalized 24 hours prior to the planned procedure. Informed consent for catheter Ablation was obtained one day before procedure.
An ECG to assess the actual rhythm, and blood tests (hemogram, renal values, and coagulation pattern and infection parameters) as well as physical and neurological examination were performed on the day of admission Physical examination also was performed again shortly before catheter ablation with special regard to neurological examination.

No changes were made to the current oral anticoagulation therapy, already started from the referring field physician. For patients taking VKA the next dose administered on the night prior to the ablation was adjusted according to the INR on admission day, reduced for INR values >3 or increased for INR<2, respectively. At the early years (2011-2015) NOACs were interrupted maximally 48h before the procedure and bridged with low molecular weight Heparin. Starting from 2015 Catheter ablation was performed under uninterrupted anticoagulation including the ablation day.

A pre-procedural transesophageal echocardiography (TEE) to exclude left atrial or left atrial appendage thrombi, was performed at the discretion of the physician to exclude left atrial thrombi. Due to symptoms and mostly heart failure these patients underwent catheter ablation procedure despite the presence of spontaneous echo contrast grade three (SEC3).

Catheter ablation was performed under conscious sedation using a combination of intravenous Propofol and Piritramid. Patients were monitored during the ablation procedure using non-invasive blood pressure measurements at 3-minute intervals, continuous pulse oximetry and continuous ECG recording.
Two trans septal sheaths were introduced via the right femoral vein, r using the modified Seldinger technique. The left femoral vein was used as vascular access for the coronary sinus catheter.

Prior to trans-septal puncture patients received 10.000 IE unfractionated Heparin. ACT measurements were done every 30 minutes, targeting at an ACT>300s. The trans septal sheath was continuously flushed with heparinized saline. Removal of all sheaths followed without previously antagonizing Heparin. Local haemostasis was achieved through local manual compression for 20-25 min and subsequent femoral compression bandage for 6-8 hours. Post ablation neurological examination showing a neurological deficit or delayed awakening would led to immediate cerebral imaging. Oral anticoagulation was interrupted in cases of intracerebral or other clinically relevant or major bleedings, otherwise oral anticoagulation was continued, especially without pauses in case of clinical TIA, stroke or another thromboembolic event.

A routine ECG control and blood tests as well as physical and neurological evaluation were performed on the post ablation day. Routine echocardiography to exclude pericardial effusion was performed first at the time of sheaths' removal and a second time 24 hours after the ablation procedure. Patients were discharged 48h after the catheter procedure in case of an uncomplicated course.

## 2.3 Definitions and data collection

Patients who underwent catheter ablation for atrial fibrillation were extracted from the database of all patients undergoing catheter ablation in Konstanz. Further information for all patients and their clinical course was extracted from the clinical charts. All data were first manually digitalised and transferred to an Excel data sheet.

The following data obtained from the ablation protocol and the hospital patient chart were obtained: Body mass index (BMI) is calculated according to the formula weight(kg)/height($m^2$). The New York Heart Association (NYHA) functional classification (43) had been assessed either from the clinician notes or obtained from reading the anamnesis and the physical examination.
The indication for catheter ablation was taken from the ablation protocol. To ensure the diagnosis and specifically determine if it was paroxysmal or persistent AF, the documented admission ECG and medical history of the patient were taken in consideration.

Paroxysmal atrial fibrillation is defined as AF that began suddenly and with a shorter duration then 7 days, whereas persistent AF is defined as duration of AF longer than one week.
Arterial hypertension is defined as blood pressure measurements >140/90mmHg or ongoing antihypertensive therapy. Data regarding diabetes mellitus and its therapy, coronary artery disease, prior stroke or TIA or prior bleeding were collected from the patient clinical medical history. Only patients with a prior documented diagnosis of hyperlipidemia were defined as so. Patients who take statin intake for secondary prophylaxis were excluded from the definition of hyperlipidemia.
Renal impairment was assessed based on the plasma Creatinine and estimated glomerular filtration rate (GFR) was calculated according to MDRD formula at the moment of hospitalisation. Medical history of prior acute and chronic renal impairment, as well hepatic impairment were documented mostly from prior diagnostic.

The presence of other pathologies and characteristics such as other vascular atherosclerosis or anemia, relevant for calculating $CHA_2DS_2$-VASC score and HAS BLEED were also collected from the patient medical history.

Afterwards $CHA_2DS_2$-VASC-Score and HAS-BLEED score were calculated according to the following criteria:

**$CHA_2DS_2$-VASC Score:**

**C** Congestive heart failure or left ventricular disfunction 1 Point
**H** Blood pressure above 90/140mmHg or hypertension treated with medication 1 Point
**$A_2$** Age ≥75 years 2 Points
**D** Diabetes mellitus 1 Point
**$S_2$** Prior stroke or TIA or thromboembolism 2 Points
**V** Vascular Disease 1 Point
**A** Age 65-74 years 1 Point
**Sc** Female sex 1 Point

**HAS-BLED Score:**

**H** Hypertension 1 Point
**A** Abnormal renal function, abnormal liver function 1 Point
**S** Prior history of stroke 1 Point
**B** Prior major bleeding or predisposition to bleeding. 1 Point
**L** Labile INR 1 Point
**E** Age >65 years 1 Point
**D** Prior drug or alcohol abuses, use of antithrombotic therapy 1 Point

The transoesophageal echocardiographies echocardiography recordings were analysed and presence of spontaneous echo contrast (SEC) was classified on a range 1-3 with SEC 3 defined as moderate to severe.

All the data regarding catheter ablation procedure such as duration of the procedure, intraprocedural heparin doses, activated clotting time (ACT) as well as anticoagulation

regime such as pause of oral anticoagulation (OAC), dose of OAC at the time of ablation and bridging were collected from the printed intraoperative protocols and printed patient records.

Definition of the primary outcome:
Thromboembolic events included stroke, transient ischemic attack or other thromboembolic events. Patients were followed on an in-hospital basis for at least the next 48 hours after catheter ablation. The neurological examination, if not completely inconspicuous was followed by cerebral imaging with cranial computed tomography (CCT, rule out bleeding) and magnetic resonance imaging (MRI) including diffusion weighted NMRI and a complete neurologic work up by an experienced neurologist. Clinically well-described TIAs with inconspicuous CCT or MRI were considered part of the efficacy outcome.

Bleeding was classified according to the International Society of Thrombosis and Haemostasis (ISTH)(44). Regarding the ISTH classification, minor bleedings are self-terminated bleedings that do not require treatment. As non-major but clinically relevant (NMCR) are considered bleeding complications that prolong hospitalisation due to increased level of care, or with haemoglobin reduction<2 units, but no major surgery. Major bleedings are bleeding complications that require transfusion because of haemoglobin reduction>2 points, major surgery or haemodynamic support. For example, a pseudoaneurysm that required surgery was classified as major bleeding. If it could be successfully corrected through thrombin injection and no transfusions were required, then the event was categorised as NMCR bleeding complication.

Data regarding the presence of pericardial effusion or pericardial tamponade were echocardiographic. Data regarding arteriovenous fistula or pseudoaneurysm of femoral artery were obtained from sonographies and sometimes from pelvic computed tomography (CT).

## 2.4 Statistical analysis

The database was created on Microsoft Excel. The patient´s data were collected on a computer inside the hospital in a pseudonymized way. Every patient received an identification number, in order to allow the identification of a patient at any given time if questions arose after data assessment
For statistical analysis SPSS, Statistics (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk and Version 29.0.0.0, NY: IBM Corp.) were used.

Descriptive statistics are reported as mean values and standard deviations for continuous data and frequencies with respective percentages for nominal variables (dichotomic data). The parametric test chi-square, is used for the comparison of dichotomic variables. To compare means for the continuous variables one-way ANOVA test was used. A p-value $\leq 0.05$ is considered statistically significant.

Furthermore, in order to assess the impact of other exploratory variables on our outcomes, logistic regression (logit) for some of the possible explanatory variables is performed. Afterward the odds ratio is calculated from the values of log-odds. A confidence level of 95% is defined. Two separate models of multivariable analysis were created for both dependent variables: thromboembolic events and any bleedings. The association of similar independent variables with the two outcomes (independent variables) such as age or gender etc. was assessed through these two models.

Furthermore, for each exploratory independent variable included in the multivariable regressions above, another separate logistic regression with interaction term was performed. The interactions between each independent variable (f. ex. age, gender) with the intake of NOAC and its association to the outcomes: thromboembolic and any bleeding complications were analysed. The association was always evaluated separately for both outcomes. These data are not represented in tables but relevant OR are represented in the results or discussion section only in the text.

Microsoft Excel is used for preparing the various charts.

# 3 RESULTS

**A part of these data have been published as a manuscript in the European Heart Journal open on 20.06.2023 (53).**

## 3.1 Baseline and clinical characteristics of the patients

We analysed the data of 1735 consecutive patients that underwent 2219 catheter ablation of atrial fibrillation from January 2011 until May 2017 at the Herz-Zentrum Bodensee, Konstanz, Germany (Table 1).

The mean age of the patient population was 63.3 years and 1488 (67%) were of male gender. Patients with Apixaban were older than patients in the other subgroups (mean age 65.7 years old). 72% (n 1589 of the cases) underwent catheter ablation because of symptomatic paroxysmal atrial fibrillation and 28% presented with persistent atrial fibrillation. In more than half of the cases (51%) patients had a NYHA score higher than two at the time of catheter ablation. The main comorbidity was hypertension with 60% of the cases having high blood pressure. Next in line stand coronary artery disease, Hyperlipidemia, and diabetes mellitus II. Two to five percent of the cases had a prior stroke or TIA in their clinical history.

Nearly 10% of the cases presented with renal impairment. Mostly, patients anticoagulated with Apixaban had a GFR<30 (4% of the cases). 1% of the total cases presented with GFR<30, whereas all cases with continuous dialysis were taking Phenprocoumon.

Half of the total cases presented (49%, n 1079) with a $CHA_2DS_2$-VASC score >2. Most patients taking VKA showed, in general, a $CHA_2DS_2$-VASC higher than two with 58% of the cases, whereas for Dabigatran 64% present with $CHA_2DS_2$-VASC lower or equal two.

Only 2% of the cases had a prior spontaneous bleeding. The highest rate of patients with prior bleedings were the ones under Apixaban. Differently from $CHA_2DS_2$-VASC score, only 1/3 of the cases (34%, n 758) presented with a HAS-BLED >2.

Nearly half of the patients were anticoagulated with the vitamin K-antagonist, Phenprocoumon (42%, n 929), and the other half with one of the novel oral

anticoagulants Rivaroxaban n 399 (18%) Dabigatran n 697 (31%), and Apixaban n 194 (9%). In most of the cases a full dose regimen of NOAC was used, more specifically: Rivaroxaban 20mg (n 395, 17.8%), Dabigatran 150mg (n 648, 29%), and Apixaban 5mg (n 192, 8.6%). Only in very few cases patients were anticoagulated with a reduced dose of NOAC: Rivaroxaban 15mg (n 3, 0.1%), Rivaroxaban 10mg (n 1, 0.04%), Dabigatran 110mg (n 49, 2%) and Apixaban 2.5mg (n 2, 0.1%).

Since there is no random distribution, p values among groups are in most cases <0.05 between variables. This is mostly due to the retrospective observational nature of the study.

| Demographic characteristics Mean value, n (%) | Phen. n 929 (42%) | Rivaroxaban n 399 (18%) | Dabigatran n 697 (31%) | Apixaban n 194 (9%) | Total cases n 2219 | p-value |
|---|---|---|---|---|---|---|
| *Age on Ablation* | 64,8 ±9.7 | 64.3 ±9.1 | 60.2 ±11 | 65.7 ±9.7 | 63.3±10 | 0.001 |
| *Gender male* | 600 (64) | 273 (68) | 507 (73) | 108 (56) | 1488 (67) | 0.001 |
| *BMI* | 28.5 ±7.3 | 28.6 ±5.5 | 27.4 ±5 | 27.5 ±4.9 | 28.1 ±6.2 | 0.001 |
| *Atrial Fibrillation* | | | | | | 0.001 |
| *Paroxysmal atrial fibrillation* | 607 (65) | 284 (71) | 554 (79) | 144 (74) | 1589 (72) | |
| *Persistent atrial fibrillation* | 322 (35) | 115 (29) | 143 (20) | 50 (26) | 630 (28) | |
| *NYHA >2* | 538 (58) | 174 (44) | 344 (49) | 83 (43) | 1139 (51) | 0.001 |
| *Hypertension* | 592 (64) | 239 (60) | 347 (50) | 116 (60) | 1294 (58) | 0.001 |
| *Diabetes mellitus* | | | | | | 0.012 |
| *Oral therapy* | 81 (9) | 44 (11) | 45 (6) | 19 (1) | 189 (8) | |
| *Insulin therapy* | 33 (3) | 7 (2) | 10 (1) | 4 (0,2) | 54 (2) | |
| *Coronary artery disease* | 157 (17) | 42 (10) | 76 (19) | 26 (16) | 301 (13) | 0.002 |
| *Hyperlipidemia* | 137 (15) | 60 (15) | 93 (13) | 25 (13) | 315 (14) | 0.872 |
| *Prior stroke* | 51 (5) | 24 (6) | 22 (3) | 12 (6) | 109 (5) | 0.073 |
| *Prior TIA* | 46 (5) | 7 (2) | 23 (3) | 5 (2) | 81 (4) | 0.024 |
| *CHADS VASC Score* | | | | | | 0.001 |
| *CHADS VASC ≤ 2* | 390 (42) | 206 (52) | 449 (64) | 95(49) | 1140 (51) | |
| *CHADS VASC >2* | 539 (58) | 193 (48) | 248 (36) | 99 (51) | 1079 (49) | |
| *Chronic/acute renal impairment* | | | | | | 0.001 |
| *GFR<60* | 104 (11) | 29 (7) | 42 (6) | 16 (8) | 191 (9) | |
| *GFR<30* | 7 (0,7) | 1 (0,3) | 3 (0,4) | 8 (4) | 19 (1) | |
| *Dialysis* | 5 (0,5) | 0 (0) | 0 (0) | 0 (0) | 5 (0) | |
| *Hepatic impairment* | 3 (0,3) | 0 (0) | 3 (0,4) | 5 (2) | 11 (0,5) | 0.001 |
| *Any prior bleeding* | 13 (1) | 8 (2) | 12 (2) | 12 (6) | 45 (2) | 0.001 |
| *HAS BLED Score* | | | | | | 0.001 |
| *HAS BLED ≤2* | 630 (68) | 274 (69) | 424 (61) | 133 (68) | 1461 (66) | |
| *HAS BLED >2* | 299 (32) | 125 (31) | 273 (39) | 61 (32) | 758 (34) | |

***Table1.*** *Demographic characteristics of the patients undergoing catheter ablation for cases anticoagulated with Phenprocoumon (VKA) and Rivaroxaban, Dabigatran, Apixaban (NOAC). Values are in number and percentage for categorical variables and in mean value for continuous variables.* The *p-value is calculated with Chi-Square of independence for dichotomic variables and one-way ANOVA test for continuous variables. BMI (body mass index), NYHA (New York Heart Association Functional Classification), TIA (transitory ischemic attack, GFR (glomerular filtration rate). For CHADS-VASC and HAS BLED Score see section 4.3.*

## 3.2 Catheter ablation procedure

60% of the cases undergoing catheter ablation of atrial fibrillation received transesophageal echocardiography prior to the procedure.

Spontaneous echo contrast grade 3 (severe or moderate) was detected in 6% of the total cases. Patients under VKA had more spontaneous echo contrast grade 3 (n 81, 9%).

In two-third of the cases, radiofrequency ablation was performed, 66% of cases underwent a first ablation procedure, 25% underwent a redo procedure and 9% of cases had a second redo intervention due to symptomatic recurrences.

The mean duration of catheter ablation was 149±56 min. The lowest Heparin requirements to reach the target ACT were observed in cases under Phenprocoumon therapy (9370±5526 IU).

Intraoperative cardioversion was necessary for 710 (32%) of the total cases.

In one-third of the cases, oral anticoagulation was interrupted on the ablation day and for at least the next 48h. During this time bridging therapy with LMWH followed.

The most interrupted agents before catheter ablation were VKA and Dabigatran with respectively 26% and 64% of the cases compared to Rivaroxaban and Apixaban with respectively 4% and 1%, (Table 2.).

| **Procedural characteristics, Mean value, n (%)** | **Phen. n 929 (42%)** | **Rivaroxaban n 399 (18%)** | **Dabigatran n 697 (31%)** | **Apixaban n 194 (9%)** | **Total Cases n 2219** | **p-value** |
|---|---|---|---|---|---|---|
| *Cryo-Balloon ablation* | 167 (18) | 119(30) | 214(31) | 71 (37) | 571 (26) | 0.001 |
| *RF-Ablation* | 762 (82) | 280(70) | 483(69) | 123 (63) | 1648 (74) | |
| *Pulmonary vein isolation* | | | | | | 0.002 |
| *First PVI* | 561 (60) | 275 (70) | 488 (70) | 134 (69) | 1458 (66) | |
| *Re-PVI* | 271 (29) | 95 (24) | 153 (22) | 44 (23) | 563 (25) | |
| *>2 PVI* | 97 (11) | 29 (6) | 56 (8) | 16 (8) | 198 (9) | |
| *Transoesophageal echocardiography* | 621 (67) | 194 (24) | 409 (59) | 110 (57) | 1334 (60) | 0.001 |
| *Spontaneous echo contrast (SEC3)* | 81 (9) | 18 (5) | 23 (3) | 13 (7) | 135 (6) | 0.001 |
| *Total Heparindosis during ablation (IU)* | 9370±5526 | 14041±5531 | 13356±7434 | 13992±4223 | 11847±6600 | 0.001 |
| *Duration of catheter ablation (minutes)* | 169±57 | 131±53 | 133±74 | 121±49 | 149±56 | 0.001 |
| *ACT>300s* | 749 (80) | 297 (74) | 489 (70) | 130 (67) | 1665 (75) | 0.001 |
| *Intraoperative cardioversion* | 339 (36) | 114 (29) | 206 (30) | 51 (26) | 710 (32) | 0.001 |
| *Interruption of anticoagulation* | 226 (26) | 14 (4) | 437 (63) | 2 (1) | 679 (30) | 0.001 |

**Table 2.** *Procedural characteristics of cases undergoing catheter ablation of atrial fibrillation under Phenprocoumon (VKA) and Rivaroxaban, Dabigatran, Apixaban (NOAC) in numbers and percentages for categorical variables and mean values with standard deviation for continuous variables. The p-value is calculated with Chi-Square of independence for dichotomic variables and one-way ANOVA test for continuous variables. RF (Radiofrequency), Spontaneous echo contrast grade 3 (SEC 3), Activated clotting time (ACT).*

## 3.3 Comparison of baseline and clinical characteristics of patients treated with Phenprocoumon versus NOAC

Patients taking Phenprocoumon were compared to a group of patients receiving novel oral anticoagulation therapy (Chart 1). More females were taking Phenprocoumon (36%) as compared to NOAC (32%), (p=0.036). Patients taking Phenprocoumon (64.8 ±9.7) were older than patients treated with one of the NOACs (62.5 ±10.5, p<0.001). Paroxysmal atrial fibrillation was more frequent for the cases receiving NOAC compared to the ones with Phenprocoumon (76% vs.65%, p=0.04), whereas no difference in both groups could be observed regarding persistent atrial fibrillation (24% vs. 35% p=0.7), respectively. The patients taking Phenprocoumon presented more often with NYHA >2 (p<0.001), hypertension (p<0.001), diabetes mellitus (p=0.014) and coronary artery disease (p<0.001). Prior stroke occurred with similar rates among the two groups (p=0.285).

Patients with Phenprocoumon seem to be sicker in general with a $CHA_2DS_2$ -VASC>2 for 58% of the cases compared to 42% of the cases with NOAC (p<0.001) whereas a HAS-BLED >2 is more frequent on cases under NOAC (36% vs. 34%, p<0.01). Significantly more cases with renal impairment were treated with a VKA (12%) compared to NOAC (7%, p<0.001). A higher tendency for the patients with NOAC to have had prior bleeding is seen (p=0.075).

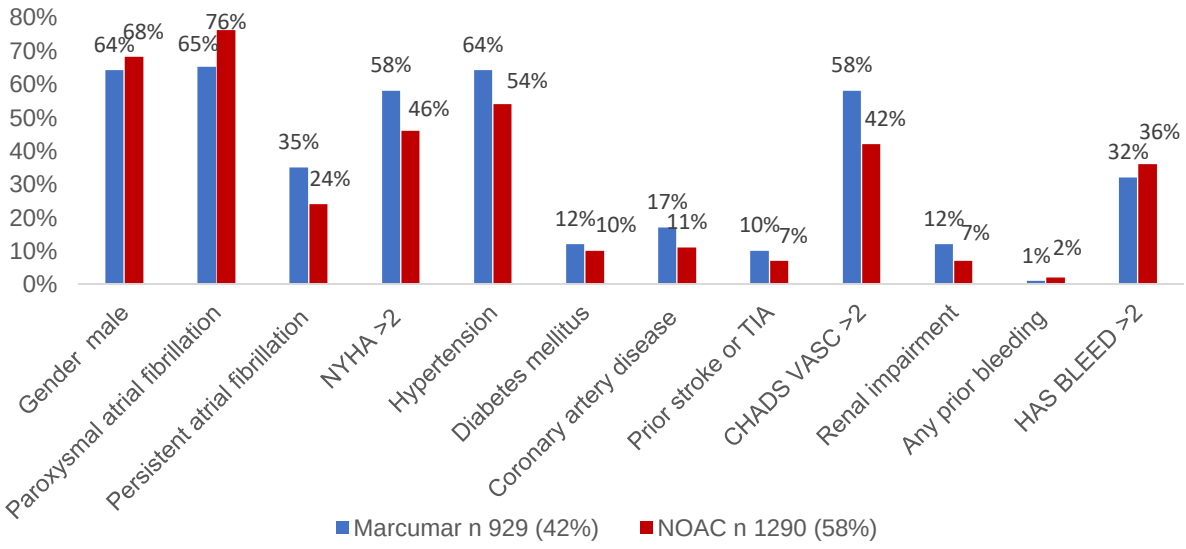


***Chart 1.*** *Demographic characteristics in rates (%) for Phenprocoumon (VKA) and all NOAC*

## 3.4 Demographic and clinical characteristics of patients with a postprocedural thromboembolic event

37 thromboembolic events (TE) occurred among all catheter ablation procedures (1.6%). The cases that had a periprocedural thromboembolic event (stroke or TIA) were slightly older when compared with the ones that did not (p=0.132).

There was a significant gender difference regarding the occurrence of a thromboembolic event (2, 8% females vs. 1% males, p=0.004).

The group with thromboembolic complications showed a similar comorbidity profile compared to the cohort without thromboembolic events within 48h post catheter ablation. The cases with thromboembolic complications had similar NYHA scores and the same frequency of hypertension, diabetes mellitus, coronary artery disease, prior stroke or prior TIA as the ones without (for p-values see Table 3). Both groups presented with a similar $CHA_2DS_2$-VASC scores (p=0.174) as well as HAS BLED scores (p=0.718).

2/3 of the patients where a thromboembolic event occurred underwent catheter ablation because of paroxysmal atrial fibrillation and 1/3 had persistent atrial fibrillation with no significant difference between both groups.

| | Thromboembolic complications n and % | | | |
|---|---|---|---|---|
| **Demographic characteristics Mean value, n (%)** | **yes n 37 1.6 (%)** | **no n 2182 98.4 (%)** | **Total cases n 2219 (%)** | **p-value** |
| *Age on Ablation* | 65.9±12.7 | 63.3±10.2 | 63.3±10.2 | 0.132 |
| ***Gender male*** | **16 (43)** | **1472 (67)** | **1488(67)** | **0.004** |
| *BMI* | 27±4 | 28.14±6 | 28.1±6.2 | 0.275 |
| *Atrial Fibrillation* | | | | 0.838 |
| *Paroxysmal atrial fibrillation* | 27 (73) | 1562 (71) | 1589(72) | |
| *Persistent atrial fibrillation* | 10 (27) | 620 (29) | 630(28) | |
| *NYHA >2* | 20 (54) | 1119 (51) | 1139(51) | 0.688 |
| *Hypertension* | 21 (57) | 1273 (58) | 1294(58) | 0.992 |
| *Diabetes mellitus* | | | | 0.398 |
| *Oral therapy* | 2 (5) | 187 (8) | 189(8) | |
| *Insulin therapy* | 2 (5) | 52 (24) | 54(2) | |
| *Coronary artery disease* | 4 (11) | 297 (14) | 301(13) | 0.490 |
| *Hyperlipidemia* | 3 (8) | 312 (14) | 315(14) | 0.595 |
| *Prior stroke* | 3 (8) | 106 (5) | 109(5) | 0.338 |
| *Prior transitory ischemic attack* | 1 (3) | 80 (4) | 81(4) | 0.778 |
| *CHADS VASC Score* | | | | 0.174 |
| *CHADS VASC ≤2* | 14 (38) | 1128 (52) | 1140(51) | |
| *CHADS VASC >2* | 23 (62) | 1056 (48) | 1079(49) | |
| *Chronic/acute renal impairment* | | | | 0.559 |
| *GFR<60* | 2 (5) | 189 (9) | 191(9) | |
| *GFR<30* | 1 (3) | 18 (1) | 19(1) | |
| *Dialysis* | 0 (0) | 5 (0.3) | 5(0) | |
| *Hepatic impairment* | 0 (0) | 11 (0.5) | 11(0,5) | 0.669 |
| *Any prior bleeding* | 0 (0) | 45 (2) | 45(2) | 0.384 |
| *HAS BLED* | | | | 0.718 |
| *HAS BLED ≤2* | 32 (86) | 1429 (65) | 1461(66) | |

| | | | |
|---|---|---|---|
| *HAS BLED >2* | 5 (14) | 753 (35) | 758(34) |

***Table3.*** *Demographic characteristics of the patients undergoing catheter ablation for cases presenting with a thromboembolic event (TE) and without. Values are in number and percentage for categorical variables and in mean value for continuous variables.* The *p-value is calculated with Chi-Square of independence for dichotomic variables and one-way ANOVA test for continuous variables. BMI (body mass index), NYHA (New York Heart Association Functional Classification), TIA (transitory ischemic attack), GFR (glomerular filtration rate). For CHADS-VASC and HAS BLED Score see section 4.3.*

## 3.5 Demographic and clinical characteristics of patients with periprocedural bleeding complications

Bleeding complications occurred in total of 285 (12, 8%) cases undergoing catheter ablation. Patients with bleeding complications were older with a mean age 65.9±9.5 compared to the non-bleeding group ($p<0.001$). The female gender had a two-times higher bleeding complication rate with 1, 7% compared to 1% male gender ($p<0.001$).

Patients with renal impairment (cut off GFR <60) showed a higher risk of bleeding compared to those with normal renal function ($p=0.038$).

Other comorbidities such as NYHA score, hypertension, prior stroke, diabetes mellitus, etc. were distributed similarly between both groups.

$CHA_2DS_2$- VASC score and HAS BLED score did not show a relevant difference when comparing patients where a bleeding complication occurred to ones without, (Table 4).

| Demographic characteristics | Bleeding complications, n and % | | | |
|---|---|---|---|---|
| | yes n 285 | no n 1934 | Total cases | |
| Mean value, n (%) | 12.8 (%) | 87.2 (%) | n 2219 (%) | p-value |
| ***Age on Ablation*** | **65.9±9.5** | **62.9±10.3** | **63.3 ±10.2** | **0.001** |
| ***Gender male*** | **157 (55)** | **1331 (68)** | **1488(67)** | **0.001** |
| *BMI* | 27.72±4.7 | 28.18±6.3 | 28.1±6.1 | 0.247 |
| *Atrial Fibrillation* | | | | 0.622 |
| *Paroxysmal atrial fibrillation* | 202 (71) | 1387 (72) | 1589(72) | |
| *Persistent atrial fibrillation* | 83 (29) | 547 (28) | 630(28) | |
| *NYHA >2* | 158 (55) | 981 (51) | 1139(51) | 0.397 |
| *Hypertension* | 166 (58) | 1128 (58) | 1294(58) | 0.929 |
| *Diabetes mellitus* | | | | 0.163 |
| *Oral therapy* | 31 (11) | 158 (8) | 189(8) | |
| *Insulin therapy* | 4 (1) | 50 (2) | 54(2) | |
| *Coronary artery disease* | 30 (10) | 271 (14) | 301(13) | 0.221 |
| *Hyperlipidemia* | 42 (15) | 273 (14) | 315(14) | 0.888 |
| *Prior stroke* | 8 (3) | 101 (5) | 109(5) | 0.078 |
| *Prior transitory ischemic attack* | 13 (5) | 68 (4) | 81(4) | 0.380 |
| *CHADS VASC Score* | | | | 0.072 |
| *CHADS VASC ≤2* | 125 (44) | 1015 (52) | 1140(51) | |
| *CHADS VASC >2* | 160 (56) | 919 (48) | 1079(49) | |
| ***Chronic/acute renal impairment*** | | | | **0.038** |
| *GFR<60* | 37 (13) | 154 (8) | 191(9) | |
| *GFR<30* | 3 (1) | 16 (1) | 19(1) | |
| *Dialysis* | 1 (0.3) | 4 (0.2) | 5(0) | |
| *Hepatic impairment* | 3 (1) | 8 (0.4) | 11(0,5) | 0.152 |
| *Any prior bleeding* | 3 (1) | 42 (2) | 45(2) | 0.211 |
| *HAS BLED* | | | | 0.067 |
| *HAS BLED ≤2* | 240 (84) | 1221 (63) | 1461(66) | |
| *HAS BLED >2* | 45 (15) | 713 (36) | 758(34) | |

***Table 4.*** *Demographic characteristics of the patients undergoing catheter ablation for cases presenting with bleeding complications and without. Values are in number and percentage for categorical variables and in mean value for continuous variables.* The *p-value is calculated with Chi-Square of independence for dichotomic variables and one-way ANOVA test for continuous variables. BMI (body mass index), NYHA (New York Heart Association Functional Classification), TIA (transitory ischemic attack), GFR (glomerular filtration rate). For CHADS-VASC and HAS BLED Score see section 4.3.*

## 3.6 Comparison of procedural data regarding Phenprocoumon versus NOAC therapy

Cryo-balloon ablation was more frequently performed in patients on treatment with NOAC (31%) compared to VKA (18%), p<0.001. There was no difference between the frequency of a first pulmonary vein isolation or a redo procedure among the two groups (Chart 2.).
Both groups, NOAC and VKA patients, underwent at similar rates preprocedural TEE. Cases under Phenprocoumon presented more spontaneous echo contrast (9%) compared to cases under NOAC (4%), p<0.001.

Intraoperative cardioversion was performed more often on the Phenprocoumon group compared to NOAC (36% vs. 29%, p<0.001).

NOACs were more frequently interrupted prior to catheter ablation than Phenprocoumon (34% vs. 26%, p<0.001).

The duration of the intervention was significantly longer for the Phenprocoumon group with 169±57 minutes compared to 134±57 minutes for NOAC, p<0.001. All in all, the total intraoperative administered Heparin was higher for the cases treated with one of the direct oral anticoagulants with 13632±6734 IU, <0.001.

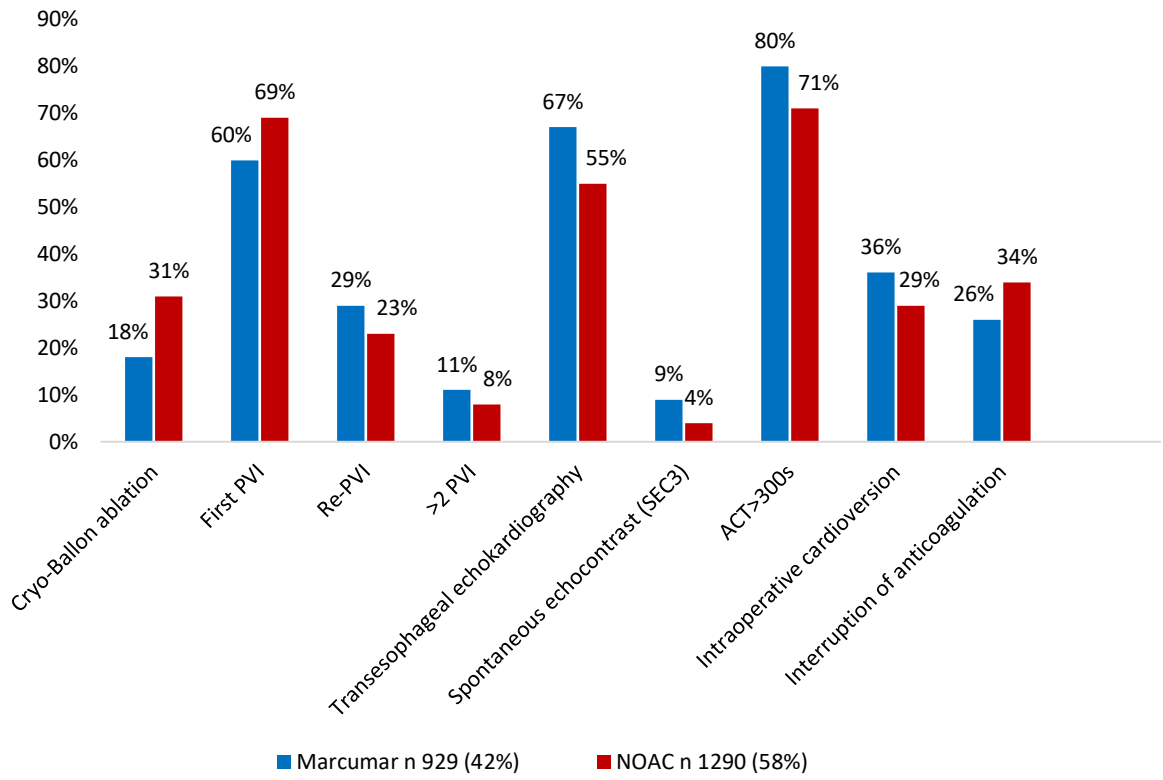


***Chart 2.*** *Procedural characteristics in rates (%) for Phenprocoumon (VKA) and all NOAC.*

## 3.7 Comparison of procedural data and thromboembolic events

| | Thromboembolic events, n and % | | | |
|---|---|---|---|---|
| **Procedural characteristics** | **yes n 37 1.6 (%)** | **no n 2182 98,4 (%)** | **Total cases n 2219, (%)** | **p-value** |
| *Cryo-Balloon ablation* | 4 (11) | 567 (26) | 571(26) | 0.392 |
| *RF-ablation* | 32 (86) | 1616 (74) | 1648(74) | |
| *Pulmonary vein isolation* | | | | 0.692 |
| *First PVI* | 27 (73) | 1431 (65) | 1458(66) | |
| *Re-PVI* | 7 (19) | 556 (25) | 563(25) | |
| *>2 PVI* | 2 (5) | 196 (9) | 198(9) | |
| *Transesophageal echocardiography* | 25 (67) | 1309 (60) | 1334(60) | 0.707 |
| *Spontaneous echo contrast (SEC3)* | 3 (8) | 132 (6) | 135(6) | 0.569 |
| *Total Heparindosis during ablation IU* | 10388±4592 | 11871±2183 | 11847±6600 | 0.181 |
| ***Duration of catheter ablation (minutes)*** | **180±69** | **148±55** | **149±56** | **0.001** |
| *ACT>300s* | 31 (83) | 1634 (77) | 1665(75) | 0.122 |
| ***Intraoperative cardioversion*** | **21 (56)** | **689 (18)** | **710(32)** | **0.001** |
| *Interruption of anticoagulation* | 16 (43) | 663 (30) | 679 (30) | 0.069 |

**Table 5.** *Procedural data of cases undergoing catheter ablation of atrial fibrillation presenting with thromboembolic events and without, in numbers and percentages for categorical variables and mean values with standard deviation for continuous variables. The p-value is calculated with Chi-Square of independence for dichotomic variables and one-way ANOVA test for continuous variables. RF (Radiofrequency), Spontaneous echo contrast grade 3 (SEC 3), Activated clotting time (ACT).*

Thromboembolic events occurred with similar rates regardless of the ablation procedure (1% cryo-balloon vs.1,7% radiofrequency, p=0.392).
Rates of first catheter ablation or a redo intervention were similar regardless occurrence of the thromboembolic event (p=0.692). Spontaneous echocontrast grade 3 or higher was present on 8% of the cases where a thromboembolic event occurred with no difference compared to inconspicuous TEE (p=0.569).

Total given intraoperative dose of Heparin given did not differ among the two groups.
The duration of catheter ablation was significantly longer in patients with a thromboembolic event (p<0.001).

There are significantly more thromboembolic events when intraoperative cardioversion was performed (cardioversion rates: 56% vs 16%, p=0.001), Table 5.

The interruption of oral anticoagulation before catheter ablation procedure showed a trend of leading to higher thromboembolic events, with 2,3% vs 1% rates of thromboembolic events in interrupted vs uninterrupted oral anticoagulation respectively (p=0.069).

Additional analysis showed that uninterrupted oral anticoagulation with a NOAC showed significantly lower rates of thromboembolic events (0.5%) compared to the Phenprocoumon group (2.6%), p=0.05.

## 3.8 Comparison of procedural data and bleeding complications

Bleeding complications occurred with similar rate among patients undergoing radiofrequency ablation (n 216, 13%) versus cryo-balloon-ablation (n 69, 12%), p=0.940.
Bleeding rates were not significantly different between first ablation procedures and re-procedures. (p=0.933).

The total given Heparindosis during ablation (p=0.510) as well as the duration of catheter ablation (p=0.124) did not differ between the cases with a bleeding complication and the ones without. Especially, the group with an intraoperative ACT >300s did not show higher bleeding complication rate (p=0.68).

Bleeding occurred significantly more often when oral anticoagulation therapy was interrupted (48% vs. 28%, p<0.001), Table 6.

The interruption of oral anticoagulation led to an increase in postprocedural bleeding in both groups of anticoagulants similarly (Phenprocoumon 21% vs. NOAC 18%), p=0.07.

| Procedural characteristics | Bleeding complications, n and % yes n 285 12.8 (%) | no n 1934 87.2 (%) | Total cases n 2219, (%) | p-value |
|---|---|---|---|---|
| *Cryo-Balloon ablation* | 69 (24) | 502 (26) | 571(26) | 0.940 |
| *RF-ablation* | 216 (76) | 1432 (74) | 1648(74) | |
| *Pulmonary vein isolation* | | | | 0.933 |
| *First PVI* | 188 (66) | 1270 (66) | 1458(66) | |
| *Re-PVI* | 74 (26) | 489 (25) | 563(25) | |
| *>2 PVI* | 23 (8) | 175 (9) | 198(9) | |
| *Transoesophageal echocardiography* | 190 (67) | 1144 (59) | 1334(60) | 0.005 |
| *Spontaneous echo contrast (SEC3)* | 21 (7) | 114 (6) | 135(6) | 0.331 |
| *Total Heparindosis during ablation IU* | 11607±4987 | 11883±1934 | 11847±6600 | 0.510 |
| *Duration of catheter ablation (minutes)* | 154±55 | 148±56 | 149±56 | 0.124 |
| *ACT>300s* | 211 (74) | 1454 (75) | 1665(75) | 0.676 |
| *Intraoperative cardioversion* | 83 (29) | 627 (32) | 710(32) | 0.263 |
| ***Interruption of anticoagulation*** | **137 (48)** | **542 (28)** | **679 (30)** | **0.001** |

**Table 6.** *Procedural data of cases undergoing catheter ablation of atrial fibrillation presenting with bleeding complications and without, in numbers and percentages for categorical variables and mean values with standard deviation for continuous variables. P-value is calculated with Chi-Square of independence for dichotomic variables and one-way ANOVA test for continuous variables. Spontaneous echo contrast grade 3 (SEC 3), Activated clotting time (ACT).*

## 3.9 Clinical outcomes of patients under Phenprocoumon versus NOAC

| Outcomes in n and (%) | Phen.n 929 (42%) | NOAC n 1290 (58%) | Total cases n 2219 and (%) | p-value |
|---|---|---|---|---|
| **Thromboembolic events** | **21 (2.2)** | **16 (1.2)** | **37 (1.6)** | **p=0.04** |
| TIA | 12 (1.3) | 11 (0.8) | 23 (1) | p=0.3 |
| **Stroke** | **10 (1)** | **4 (0.3)** | **14 (0.6)** | **p=0.02** |
| Bleeding events in total | 122 (13) | 163 (12.6) | 285 (12.8) | p=0.7 |
| **Minor bleeding** | **87 (9.3)** | **119 (9.2)** | **206 (9.2)** | **p=0.01** |
| NMCR bleeding | 30 (3.3) | 32 (2.5) | 62 (2.7) | p=0.4 |
| Major bleeding | 5 (0.5) | 12 (0.9) | 17 (0.8) | p=0.4 |

**Table 7.** *Outcomes in number and percentage for Phenprocoumon (VKA) and the NOAC. P-value is calculated with Chi-square. TIA (transitory ischemic attack), NMCR (non-major but clinically relevant).*

37 (1.6%) thromboembolic events occurred among 2219 ablation procedures in total. 2/3 of the thromboembolic cases were TIA and 1/3 of the cases suffered a stroke.

Patients on Phenprocoumon therapy had significantly more thromboembolic events compared to patients treated with NOAC (n 21, 2.2% vs. n 16, 1.2% respectively), p= 0.04.
The statistical significance is attributed specifically to the frequency of strokes in the Phenprocoumon group vs NOAC group (1% vs 0.3 % p= 0.02) respectively with no difference in regard to the occurrence of a TIA (p=0.3).

There was a total of n 285, 12.8% bleeding complications, with 72% being minor bleedings. Bleeding complications after catheter ablation were comparable between both groups (Phenprocoumon n 122, 13% and with NOAC n 163, 12.6%), p=0.7.

Minor bleedings occurred more frequently in the Phenprocoumon group, whereas for non-major but clinically relevant (NMCR) and major bleedings there was no difference among both groups.

## 3.10 Comparison of bleeding and thromboembolic events among different anticoagulant agents

| Outcomes in n and (%) | Phen. n 929 (42%) | Rivaroxaban n 399 (18%) | Dabigatran n 697 (31%) | Apixaban n 194 (9%) | Total cases n 2219 and (%) | p-value |
|---|---|---|---|---|---|---|
| **Thromboembolic events in total** | **21 (2.2)** | **3 (0.7)** | **11 (1,5)** | **2 (1)** | **37 (1.6)** | **p=0.07** |
| TIA | 12 (1.3) | 1 (0.2) | 9 (1.2) | 2 (1) | 23 (1) | p=0.5 |
| **Stroke** | **10 (1)** | **2 (0.5)** | **2 (0.3)** | **0 (0)** | **14 (0.6)** | **p=0.02** |
| Bleeding events in total | 122 (13) | 38 (9.5) | 102 (14) | 23 (12) | 285 (12.8) | p=0.09 |
| Minor bleeding | 87 (9.3) | 27 (7) | 78 (11) | 14 (7) | 206 (9,2) | p=0.07 |
| **NMCR bleeding** | **30 (3.3)** | **9 (2.3)** | **18 (2.5)** | **5 (2,6)** | **62 (2.7)** | **p<0.05** |
| **Major bleeding** | **5 (0.5)** | **3 (0.8)** | **6 (0.08)** | **3 (1.5)** | **17 (0.8)** | **p<0.05** |

**Table 8.** *Outcomes in number and percentage for Phenprocoumon (VKA) and the Rivaroxaban, Dabigatran, and Apixaban separately. P-value is calculated with Chi-square. TIA (transitory ischemic attack), NMCR (non-major but clinically relevant).*

Thromboembolic events occurred with a similar frequency regardless of the type of anticoagulation agent, p=0.07 (Table 8.). However, the rate of stroke did not differ significantly between the NOAC, with a rate of 0.5% for Rivaroxaban, 0.3% for Dabigatran, and no strokes for Apixaban. compared to 1% for Phenprocoumon (p=0.02).

The total bleeding rates were comparable among the different anticoagulation agents (p=0.09). However, there is a significant difference between groups in terms of NMCR with Phenprocoumon 3.3%, Rivaroxaban 2.3%, Dabigatran 2.5%, Apixaban 2.6% (p<0.05) and major bleedings with Phenprocoumon, 0.5%, Rivaroxaban 0.8%, Dabigatran 0.08%, Apixaban 1.5% (p<0.05) (Chart 3).

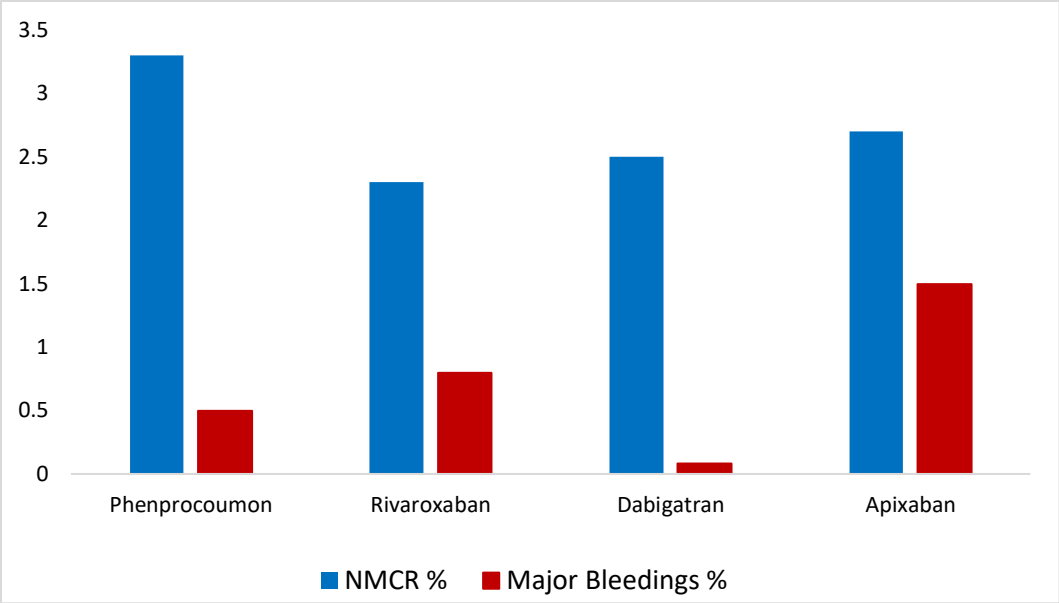


***Chart 3.*** *Percentage of NMCR and major Bleedings for Phenprocoumon (VKA), Rivaroxaban, Dabigatran, and Apixaban.*

## 3.11 Multivariable analysis for thromboembolic and bleeding complications

**Thromboembolic complications:**

| Independent variables | ß | Standard error | OR | CI | p-value |
|---|---|---|---|---|---|
| *Age on Ablation* | 0.011 | 0.029 | 1.011 | 0.956-1.070 | 0.693 |
| *Gender Male* | -0.557 | 0.411 | 0.573 | 0.256-1.282 | 0.175 |
| *Persistent atrial fibrillation* | -0.199 | 0.157 | 0.820 | 0.603-1.114 | 0.204 |
| *NYHA* | -0.364 | 0.335 | 0.695 | 0.360-1.341 | 0.278 |
| *Hypertension* | -0.208 | 0.559 | 0.813 | 0.272-2.431 | 0.710 |
| *Diabetes mellitus* | 0.040 | 0.440 | 1.040 | 0.439-2.466 | 0.928 |
| *Coronary artery disease* | -0.424 | 0.369 | 0.654 | 0.317-1.349 | 0.251 |
| *Prior stroke* | 0.173 | 0.827 | 1.189 | 0.235-6.012 | 0.834 |
| *Prior transitory ischemic attack* | -0.979 | 1.192 | 0.376 | 0.036-3.891 | 0.412 |
| ***$CHA_2DS_2$-VASC Score*** | **0.490** | **0.248** | **1.633** | **1.004-2.655** | **0.048** |
| *HAS BLED Score* | -0.534 | 0.413 | 0.586 | 0.261-1.317 | 0.196 |
| *Chronic/acute renal impairment* | -0.010 | 0.573 | 0.990 | 0.322-3.043 | 0.986 |
| *Cryo-Balloon ablation* | -0.798 | 0.587 | 0.450 | 0.143-1.423 | 0.174 |
| *Re-PVI* | -0.358 | 0.326 | 0.681 | 0.359-1.288 | 0.237 |
| *Transoesophageal echocardiography* | -0.017 | 0.386 | 0.983 | 0.461-2.097 | 0.965 |
| ***Duration of catheter ablation (minutes)*** | **0.007** | **0.003** | **1.007** | **1.001-1013** | **0.027** |
| *ACT>300s* | 0.613 | 0.505 | 1.847 | 0.687-4.964 | 0.224 |
| ***Intraoperative cardioversion*** | **0.920** | **0.362** | **2.509** | **1.233-5.105** | **0.011** |
| ***Interruption of anticoagulation*** | **0.770** | **0.357** | **2.159** | **1.073-4.347** | **0.031** |

**Table 9.** *Logistic regression analysis for each possible explanatory variable (logit) regarding thromboembolic events. Afterward the odds ratio was calculated from the values of log-odds, the confidence interval is defined as 95%. NYHA (New York Heart Association Functional Classification), for $CHA_2DS_2$-VASC and HAS BLED Score see section 4.3, Activated clotting time (ACT), pulmonary vein isolation (PVI), OR (odds ratio), CI (confidence interval).*

Furthermore, regression analysis was performed to assess the association of the explanatory variables with the thromboembolic complication.

A significant predictor for a periprocedural thromboembolic event was performing an intraoperative cardioversion with p=0.011, increasing the thromboembolic risk with an OR of 2.5.

The interruption of anticoagulation significantly associated with an increased risk of thromboembolic complications (OR 2.1, p=0.031).

Duration of catheter ablation procedure associated to slightly higher risk of periprocedural thromboembolic risk (OR 1.007 per minute, p=0.027).

Increase of $CHA_2DS_2$-VASC-score increased the risk for thromboembolic complications (OR 1.6, p=0.048).

Not predictive factors for thromboembolic events were an increasing age (per one year of age increment, p=0.693), male gender (p=0.175), other comorbiditie, or HAS-BLED score (p=0.196), Table 9.

**Any bleeding complications:**

| Independent variables | ß | Standard error | OR | CI | p-value |
|---|---|---|---|---|---|
| ***Age on Ablation*** | **0.029** | **0.011** | **1.030** | **1.008-1.052** | **0.007** |
| ***Gender Male*** | **-0.460** | **0.163** | **0.631** | **0.459-0.868** | **0.005** |
| *Persistent atrial fibrillation* | 0.020 | 0.049 | 1.020 | 0.927-1.123 | 0.684 |
| *NYHA* | 0.084 | 0.131 | 1.088 | 0.841-1.406 | 0.522 |
| *Hypertension* | -0.232 | 0.204 | 0.793 | 0.531-1.184 | 0.256 |
| *Diabetes mellitus* | 0.047 | 0.181 | 1.048 | 0.735-1.495 | 0.795 |
| *Coronary artery disease* | -0.165 | 0.132 | 0.847 | 0.654-1.098 | 0.211 |
| *Prior stroke* | -0.776 | 0.429 | 0.460 | 0.198-1.068 | 0.071 |
| *Prior transitory ischemic attack* | 0.098 | 0.387 | 1.103 | 0.517-2.353 | 0.801 |
| *$CHA_2DS_2$-VASC Score* | -0.027 | 0.102 | 0.937 | 0.796-1.189 | 0.790 |
| *HAS BLED Score* | 0.101 | 0.136 | 1.106 | 0.847-1445 | 0.457 |
| *Chronic/acute renal impairment* | 0.126 | 0.190 | 1.134 | 0.781-1.647 | 0.509 |
| *Cryo-Balloon ablation* | -0.101 | 0.160 | 0.904 | 0.660-1.238 | 0.530 |
| *Re-PVI* | -0.017 | 0.112 | 0.983 | 0.789-1.225 | 0.881 |
| *Transesophageal echocardiography* | 0.256 | 0.140 | 1.291 | 0.981-1.700 | 0.068 |
| *Duration of catheter ablation (minutes)* | 0.001 | 0.001 | 1.001 | 0.998-1.003 | 0.656 |
| *ACT>300s* | -0.072 | 0.154 | 0.930 | 0.688-1.258 | 0.640 |
| *Intraoperative cardioversion* | -0.216 | 0.149 | 0.805 | 0.602-1.078 | 0.145 |
| ***Interruption of anticoagulation*** | **0.896** | **0.137** | **2.449** | **1.871-3.205** | **<0.001** |

**Table 10.** *Logistic regression with interaction term analysis for each possible explanatory variable (logit) regarding any bleeding complication for the group under NOAC compared to VKA. Afterward the odds ratio was calculated from the values of log-odds, the confidence interval is defined as 95%. NYHA (New York Heart Association Functional Classification), for $CHA_2DS_2$-VASC and HAS BLED Score see section 4.3, Activated clotting time (ACT), pulmonary vein isolation (PVI), OR (odds ratio), CI (confidence interval).*

Age associated with increased risk of any bleedings with an OR 1.020, p=0.007. Male gender was a favourable predictor reducing the risk of bleeding with an OR 0.631 (p=0.005). Patients with a history of stroke had a tendency to lower risk for bleeding complications with an OR 0.46 (p=0.071).

NYHA score (p=0.522), hypertension (p=0.256), or diabetes mellitus (p=0.795) did not significantly associate with the risk for any bleedings.

Duration of the ablation procedure (p=0.656) and ACT>300s (p=0.640) did not have an impact on the risk of bleeding.

Interruption of oral anticoagulation before ablation procedure was a strong predictor for an increased risk of bleeding (OR 2.4, p<0.001), Table 10.

# 4 DISCUSSSION

## 4.1. Demographic and procedural characteristics and impact on thromboembolism and bleeding risk

*Age and association with peri-ablation complications*

Age and comorbidities increase the risk of thromboembolic events in patients with atrial fibrillation(5). The age of the study population is concordant with other studies comparing the safety and efficacy of NOAC to VKA (Warfarin) in patients undergoing catheter ablation of non-valvular atrial fibrillation (18,19,22). In the present study, patients taking Phenprocoumon were older and reported more comorbidities than the ones on NOAC. However, when using multivariable analysis, older age and more comorbidities, did not associate to an increased risk for thromboembolic risk. In contrast, age associated to slightly higher risk of any bleedings (OR 1.030, p=0.007). Furthermore, the regression with interaction terms analysis revealed that older patients taking NOAC had a slightly higher bleeding risk (OR 1.026, p=0.002). This might be caused by the higher risk of bleeding which has been shown with dabigatran in the elderly for example in a subgroup analysis of the RELY study (33).

*Gender and association with peri ablation complications*

In our study 2/3 of the population were of male gender similar to most other studies (27–30). Female patients with atrial fibrillation have a higher risk for thromboembolic complications and mortality (6). The present study shows that patients of female gender undergoing catheter ablation were at higher risk for both thromboembolic and bleeding events. However, gender did not associate with the thromboembolic outcome (p=0.175) whereas male patients treated with NOAC had a lower risk of bleeding (OR 0.606, p=0.004). The reasons remain speculative, clinical studies comparing NOAC with Vitamin K Antagonist did not find an increased risk for bleeding in women (18,19,20).

*$CHA_2DS_2$-VASC Score and association with peri ablation complications*

Our study showed a homogeneous distribution of $CHA_2DS_2$-VASC-score for all type of anticoagulants (Phenprocoumon, Rivaroxaban, Apixaban, Dabigatran) with half of the cases presenting with $CHA_2DS_2$-VASC-score ≤2. Nevertheless, when comparing Phenprocoumon to all NOACs, patients taking Phenprocoumon had a significantly higher $CHA_2DS_2$-VASC-score>2 (Phenprocoumon 58% vs. NOAC 42%). In the multivariable analysis, the increase of $CHA_2DS_2$-VASC-score with 1 point increased thromboembolic risk (OR 1.6, p=0.048). HAS BLED did not associate with both thromboembolic and bleeding risk.

When considering the regression with interaction terms the increase of $CHA_2DS_2$-VASC-score with 1 point in the Phenprocoumon group did neither increase the thromboembolic nor the bleeding risk when compared to the increase of $CHA_2DS_2$-VASC-score with 1 point in the NOAC group. In a small-randomized study, comparing Rivaroxaban to Warfarin, the thromboembolic risk was not significantly different between the two study groups, however, thromboembolic events in this study occurred in the Warfarin group only (18). The mean $CHA_2DS_2$-VASC-score was below 2 in this study. Comparable findings were made in randomized study with Dabigatran and Warfarin although the mean $CHA_2DS_2$-VASC-score was above 2 in the study (22).

These findings question the general assumption that an increase of the $CHA_2DS_2$-VASC-score simply points to a higher risk of embolic events associated with catheter ablation of atrial fibrillation. This may in part be because the risk attributable to one point of the score varies significantly. For example, hypertension is associated with one risk point but does have a very low stroke risk, if hypertension is treated (34).

Renal impairment and association with peri ablation complications

From all NOACs, Apixaban seems to be more favourable regarding thromboembolic and bleeding risk for patients with renal impairment (45). For patients undergoing dialysis (GFR <10) oral VKA is one of the most common anticoagulation therapy (34). In our cohort, renal impairment did not increase the risk of thromboembolic events. On the other hand, more patients with chronic/acute renal impairment had bleeding

complications (13% with bleeding vs 9% no bleeding, p=0.038). Despite more bleeding events in patients with renal impairment, the multivariable analysis showed that it did not affect the risk of bleedings.

*Procedural characteristics and association with peri ablation complications*

Long procedural time increases the risk for perioperative complications(46) and this study showed an slightly increase of thromboembolic risk per minute of duration of catheter ablation (OR 1.007 per minute, p=0.027).
When adjusted for type of anticoagulation, in our study the duration of intervention did not impact the thromboembolic risk for patients taking a NOAC (p=0.24). This may be due to similar rates of achieving ACT>300s in both anticoagulant groups. In concordance with other studies (18–20) more intravenous Heparin was needed for patients treated with NOAC compared to Phenprocoumon in order to achieve an ACT>300s. The length of the ablation procedure did not significantly associate with any bleeding complications (p=0.656).

Depending on patients characteristics(47), electrical cardioversion is related to a higher thromboembolic (stroke and TIA) risk. In our patient population, intraoperative cardioversion increased the risk of thromboembolic complications (OR 2.5, p=0.011).

## 4.2. Safety and efficacy of Phenprocoumon compared to the new oral anticoagulants

*Considerations regarding the rates of total peri ablation thromboembolic events*

Phenprocoumon differs in its pharmacokinetic significantly from Warfarin, especially the elimination half-life of Phenprocoumon is at least three times as long as the elimination half-life of Warfarin. This may, after steady state of plasma levels have been reached, lead to uniform plasma levels and thus a very stable oral anticoagulant effect (17). In contrast to this desirable effect, the long elimination half-life could increase the risk of bleeding if plasma levels are too high, since the long half-life of Phenprocoumon precludes rapid dose adjustments. These differences to Warfarin necessitate clinical studies investigating the question whether clinical data obtained for the NOAC in comparison to Warfarin, are applicable to patient populations usually treated with Phenprocoumon.

In our retrospective analysis of a cohort of consecutive patients undergoing catheter ablation of atrial fibrillation, we compared patients treated with NOAC to patients treated with Phenprocoumon. The total number of thromboembolic events was 37 (1.6%), n 14 (0.6%) suffering stroke and n 23 (1%) having a TIA. The rates of thromboembolic events in our study were higher when compared to the outcome of other observational studies reporting a thromboembolic risk of 0.5-1% associated with catheter ablation of atrial fibrillation (39).

This difference may in part be due to the definition of thromboembolic events in our study as compared to the other studies. One study comparing uninterrupted Dabigatran with uninterrupted Warfarin had for example 2.1% stroke rate in the Dabigatran group and not a single TIA in both groups (25). In our study the number of TIAs was twice as high as the number of strokes, while in most studies TIAs were less than a third of the thromboembolic events (18,21,22). Included on the definition of TIA were also clinically diagnosed TIA with inconspicuous cranial computed tomography or magnetic resonance imaging.

The higher thromboembolic rates in our study could furthermore be attributed to the fact that the patient collective in our study does not stern from a randomised highly selected group of patients, but reflects the outcome of consecutive patients undergoing

catheter ablation of atrial fibrillation. The choice of anticoagulation was not always made in-hospital. Most of the patients were on an anticoagulation therapy, prescribed from the referring physician at the moment of recovery. The fact that randomisation in the above studies sometimes lacked blinded randomisation (20), could also have led to the generally lower thromboembolic rates in other studies.

In conclusion, our findings in respect to thromboembolic event are in the range of the thromboembolic event rate described by other studies (39, 50).

*Efficacy of Phenprocoumon vs. NOAC in catheter ablation of non-valvular atrial fibrillation*

We reported a significantly higher rate of thromboembolic complications in patients taking Phenprocoumon (2.2%) compared to the ones taking a NOAC (1.2%), p=0.04 showing that probably NOACs may due to their shorter half-life and steady state after intake (17) be more effective on protecting against thromboembolic complications.

The VENTURA study compared Rivaroxaban to VKA (Warfarin) post catheter ablation (18). The rates of thromboembolic events were 0% for Rivaroxaban compared to 3% for patients taking Warfarin. RE-CIRCUIT, compared Dabigatran 150mg to uninterrupted Warfarin showing 0% systemic embolies for patients treated with Dabigatran and one TIA event in the Warfarin group (22). The higher thromboembolic rates for patients treated with NOAC in our study may be due to the fact that in VENTURA patients with Rivaroxaban presented with a mean $CHA_2DS_2$-VASC Score 1.5 probably having a lower thromboembolic risk from the beginning (18). RE-CIRCUIT was designed with the aim of showing a non-inferiority regarding the safety of Dabigatran compared to Warfarin and the systemic embolies are considered only as a part of the composite endpoints (22). For Dabigatran most of the thromboembolic events in our study were TIAs (n 9) as compared to Strokes (n 2). Considering that the larger part of thromboembolic events for Dabigatran consisted in TIAs, the accurate inclusion of clinical TIAs in our study might be the reason for higher thromboembolic complications for patients treated with NOAC in our study.

All in all, the cohort of patients included (18, 22) was very small compared to our patient collective which could also have influenced our higher thromboembolic rates for NOAC in catheter ablation of atrial fibrillation.

Similar rates of thromboembolic events with our study were reported when Apixaban was compared to VKA (Warfarin) in atrial fibrillation ablation with 2% for patients treated with Apixaban and 3% for patients treated with VKA. This may be due to the fact that in this study also the silent cerebral infarction was considered as part of the primary outcome (20).

Nevertheless, the finding that the use of a NOAC can reduce the risk of thromboembolic events (stroke and TIA) compared to VKA (Phenprocoumon) is in line with the results of the other randomised trials comparing NOAC to VKA (Warfarin) indicating a preference to use NOAC to VKA in catheter ablation of non-valvular atrial fibrillation (18,22).

Smaller observational studies on the other hand, showed similar or higher thromboembolic rates in the patients treated with a NOAC (Apixaban 0% or Dabigatran 2%) when compared to the patients treated with Warfarin (0% thromboembolic events in both studies) (24,51). This may depend on the fact that the morning dose of Dabigatran before catheter ablation was left out, thus not truly reflecting the effect of uninterrupted Dabigatran therapy.

*General considerations regarding the rates of peri ablation total bleedings*

There occurred 285 (12,8%) total peri ablation bleeding complications with mostly minor bleedings ( n 206, 9,2%) and fewer NMCR bleedings (n 62, 2,7%) or major bleedings (n 17, 0.8%). These rates are similar to the RE-LY study showing 14% total bleedings for Dabigatran group vs. 16% for the Warfarin group (27). Other studies such as ROCKET-AF (28) and ARISTOTLE (29) comparing Rivaroxaban and Apixaban with VKA (Warfarin) respectively did not report the data regarding the total bleedings and concentrated their findings mostly on major bleedings. Both showed higher rates of major bleedings for NOAC and VKA when compared to the rates reported in our study. A longer follow-up in time might be the reason for this difference.

*Comparison of safety of Phenprocoumon vs. NOAC in catheter ablation of non-valvular atrial fibrillation*

Total bleeding complications occurred with similar frequency in both groups (13% Phen. vs 12,6% NOAC, p=0.7). When considering all NOACs compared to Phenprocoumon a tendency to higher minor bleeding and non-major but clinically relevant bleeding complications for Phenprocoumon could be shown. Similar bleeding rates after catheter ablation of atrial fibrillation could be shown when comparing Rivaroxaban to Warfarin in VENTURA (18) as well as Dabigatran to Warfarin in RE-CIRCUIT (22). The total bleeding rates in VENTURA were similar to the ones in our study with 17% bleedings for Rivaroxaban and 15% for the Warfarin group. In conclusion, no difference regarding bleeding risk could be shown when comparing NOAC to the VKA, Phenprocoumon with longer half-life than Warfarin.

The different patient population, trial design, dose regiments and anticoagulation agents with a different pharmacokinetic profile make a head-to-head comparison of the NOAC studies very difficult.

When considering the type of NOAC separately, the NOAC with the lowest major bleeding rate in our study was Dabigatran with 0.08% major bleedings. This findings showed a significantly lower bleeding risk for Dabigatran as compared to the major bleeding rates for patients treated with Dabigatran in RE-CIRCUIT with 1,6% major bleeding rates after catheter ablation(22). One study showed higher plasma concentrations of Dabigatran when the doses intake was delayed (52). This is a plausible explanation for the higher bleeding risk after interruption of Dabigatran in RE-CIRCUIT as compared to our study where most of the catheter ablations were performed under uninterrupted anticoagulation. Nevertheless, even in RE-CIRCUIT Dabigatran was more favourable than VKA with fewer major bleeding at 7 days after ablation procedure (22).

## 4.3 Interruption of anticoagulation on catheter ablation

The oral anticoagulation was till now days normally paused at least 24h before performing a catheter ablation of atrial fibrillation or any other ablation in the left atrium (8) especially because of pericardial tamponade risk (1-2%)(14). On the other hand the procedure has a high thromboembolic risk(8). With time observational studies showed that interruption of anticoagulation (NOAC and VKA) and bridging with LWMH increase both the risk of systemic embolies and bleedings(24,37,48).

In our study most of the ablations (2/3) were performed with uninterrupted anticoagulation. NOAC were interrupted more often than Phenprocoumon (NOAC 34% vs. Phenprocoumon 26%, $p<0.001$). When anticoagulation was interrupted, the risk of both thromboembolic and bleeding events increased in the following 48h.

Thromboembolic risk increased with OR 2.159 when anticoagulation was interrupted (more specifically: 2.3% thromboembolic events when anticoagulation was interrupted vs 1% thromboembolic events when anticoagulation was not interrupted, $p=0.06$).

In addition, the interruption of NOAC therapy increased the risk of thromboembolies significantly compared to the interruption of Phenprocoumon (OR 3.7, $p=0.016$). This could be due to the shorter half-life of NOAC and the importance of achieving a steady state depending on NOAC intake(25). It also does not seem plausible that reaching a stable plasma level of Phenprocoumon(17) could allow somehow to leave the out doses before catheter ablation.

Thromboembolic and bleeding rates in our study varied sometimes from studies considering uninterrupted anticoagulation therapy after catheter ablation (see section 6.2 for detailed explanation). This might also be due to the fact that these studies have not defined exactly what uninterrupted anticoagulation truly means. In most of studies the dose before catheter ablation was actually left out(18–22). In our study “uninterrupted” means continued anticoagulation intake also in the ablation day, which because the findings that uninterrupted anticoagulation in catheter ablation of atrial fibrillation is preferable for reducing the risk for both peri procedure thromboembolic and bleeding complications solidifies our suggestion to not interrupt anticoagulation.

Only in 2020 the European society of cardiology suggested performing catheter ablation with uninterrupted anticoagulation as a Class I indication(34). Because of these findings, further randomised studies to better clarify the best practical use of NOAC of before catheter ablation are necessary.

## 4.4 Study limitations

This is an observational retrospective analysis of consecutive patients undergoing catheter ablation of atrial fibrillation. These results do not imply causality and should be considered hypothesis generating. One of the most important limitations is the non-randomised nature of the study. To adjust for confounding factors we used the multivariate regression model(49).

The single centre character of this study limits the generalisability of the results. A time bias may have been introduced during the course of the study given differential prescription patterns while the operator´s experience increased.

Furthermore, this study observes the thromboembolic and bleeding outcomes only for the following 48h post catheter ablation. A longer follow-up in time could be of importance to better understand the risk factors leading to complications and the best anticoagulation regime for the patients.

## 4.5 Conclusions

In this observational study of consecutive patients undergoing catheter ablation of atrial fibrillation, oral anticoagulation with one of the NOACs reduced the risk of thromboembolic events compared to Phenprocoumon. Non-interrupted NOAC therapy further reduced the risk of thromboembolic complications.

Despite the better protection against thromboembolic complications, bleeding events related to catheter ablation occurred with the same frequency when using an oral anticoagulation therapy with Phenprocoumon and with the NOACs, respectively.

Uninterrupted oral anticoagulation was preferable to further reduce the risk of bleeding and /or thromboembolic events.

# 5 SUMMARY

## 5.1 English version


### Introduction

The use of novel oral anticoagulants (NOAC) in patients undergoing catheter ablation of atrial fibrillation (AF) is as effective and safe as standard Warfarin therapy. Phenprocoumon is a vitamin K antagonist (VKA) with a long elimination half-life (T ½ 110-130h) and this could further reduce the risk of thromboembolism due to more uniform plasma levels. On the other hand, this could lead to bleeding that is more difficult to control. Comparative studies between the vitamin K antagonist Phenprocoumon and the NOAC are lacking. In addition, the question arises whether uninterrupted therapy with NOAC is safe and effective. The aim of the study is to compare NOAC (Dabigatran, Apixaban and Rivaroxaban) with Phenprocoumon as well as to compare uninterrupted oral anticoagulation with interrupted anticoagulation.

### Material and methods

We performed a retrospective observational study. Between January 2011 and May 2017, 2219 catheter ablations of atrial fibrillation were performed in 1735 consecutive patients with an average mean age of 63.3 years; 1488 (67%) procedures were performed in men. 929 procedures (42%) were performed under oral anticoagulation with Phenprocoumon, 697 (31%) under Dabigatran, 399 (18%) under Rivaroxaban and 194 (9%) under Apixaban. Immediately after the market launch of NOAC, catheter ablations of atrial fibrillation were performed only after discontinuation of NOAC (n 679, 30%), periprocedural anticoagulation was performed with a low molecular weight heparin. All patients were observed under in hospital conditions for at least 48 hours after catheter ablation and a neurological examination was performed daily. In the case of neurological deficits, whether transient or persistent, a neurologist was consulted and cerebral imaging was performed.

### Results

A $CHA_2DS_2$-VASC score >2 was seen more frequently in patients with Phenprocoumon than in patients with NOAC (58% versus 42%, $p<0.001$). Also,

patients with renal failure were treated more frequently with a VKA than with a NOAC (12% vs 7% respectively, p<0.01)**.**

During the in hospital stay following catheter ablation, 37 (1.6%) thromboembolic events occurred, including 23 transient ischaemic events.

The overall risk of thromboembolic events was significantly higher in patients treated with Phenprocoumon than in patients treated with NOAC (21 versus 16 cases, 2.2% versus 1.2%, p=0.04). In particular, stroke was more frequent in patients treated with Phenprocoumon as compared to patients treated with NOAC (1% vs. 0.3% respectively, p=0.02). Uninterrupted oral anticoagulation was associated with lower rates of thromboembolic events in the NOAC group compared to the Phenprocoumon group (0.5% vs. 2.6% respectively, p=0.05). Bleeding complications (n=285, 12.8%) after ablation occurred without difference in patients treated with Phenprocoumon (n 122, 13%) and NOAC (n 163, 12.6%). There was no difference for both groups when considering the rates for minor bleedings, non-major but clinically relevant bleedings as well as major bleedings. In summary, it came to very few major bleedings with 6% of total bleeding events. Most of the bleedings were minor ones (n 206, 72%). An intraprocedural cardioversion significantly increased the thromboembolic risk (OR 1.2, p=0.012).

Age and HAS-BLED score did not measurably have an impact on thromboembolic risk.

When anticoagulation was interrupted, the risk for thromboembolic complications increased significantly (OR 2.1, p=0.013). The interruption of oral anticoagulation led to an increase of peri-procedural bleeding events in both groups with OR 2.4 (Phenprocoumon 9% versus 21%, NOAC 7% versus 18%, p=0.07). When a NOAC was interrupted the risk for bleedings increased with an OR of 2.3 (p=0.001).

## Conclusions

In this observational study of consecutive patients undergoing catheter ablation of atrial fibrillation, oral anticoagulation with one of the NOACs reduced the risk of thromboembolic events compared to Phenprocoumon.

Despite the better protection against thromboembolic complications, bleeding events related to catheter ablation occurred with the same frequency when using an oral anticoagulation therapy with Phenprocoumon and with the NOACs, respectively.

Uninterrupted oral anticoagulation was preferable to further reduce the risk of bleeding and /or thromboembolic events.

## 5.2 Deutsche Version

### Einführung

Die Gabe der neuen oralen Antikoagulanzien (NOAC) hat bei Patienten, die eine Katheterablation von Vorhofflimmern erhalten haben, die gleiche Effektivität wie die Standardtherapie mit Warfarin. Phenprocoumon ist ein Vitamin K-Antagonist (VKA), der eine lange Halbwertszeit hat (T ½ 110-130h). Dies könnte zu homogeneren Plasma-Spiegel und damit zu einer weiteren Reduktion des thromboembolischen Risikos führen. Anderseits könnte das Risiko für schwerere Blutungskomplikationen, aufgrund der schwierig zu steuernden oralen Antikoagulation mit Phenprocoumon, zunehmen.

Die Datenlage für Vergleiche zwischen Phenprocoumon und NOAC ist bisher nicht vollständig. Des Weiteren ist noch unklar, ob die ununterbrochene Einnahme von NOAC vor der Ablation sicher und effektiv ist. Das Hauptziel unserer Beobachtungstudie ist die Evaluation der Wirksamkeit und Sicherheit von NOAC (Dabigatran, Apixaban und Rivaroxaban) im Vergleich zu VKA (Phenprocoumon). Zusätzlich erlaubt der Datensatz den Vergleich einer unterbrochenen Therapie mit den oralen Antikoagulantien mit einer nicht unterbrochenen Therapie.

### Material und Methoden

Dies ist eine retrospektive Beobachtungsstudie. Zwischen Januar 2011 und Mai 2017 wurden 2219 Katheterablationen von Vorhofflimmern an 1735 Patienten mit einem mittleren Alter von 63.3 Jahren durchgeführt; 1488 (67%) davon an Männern. 929 (42%) der Prozeduren wurden bei Patienten mit VKA (Phenprocoumon) durchgeführt, 697 (31%) mit Dabigatran, 399 (18%) mit Rivaroxaban und 194 (9%) mit Apixaban. Nach der Markteinführung der NOAC wurde die Antikoagulationstherapie zunächst vor der Katheterablation pausiert (n 697, 30%), die peripozedurale Antikoagulation erfolgte dann mit Heparin (LWMH). Alle Patienten wurden nach der Ablation für mindestens 48 Stunden stationär beobachtet und täglich klinisch untersucht. Bei fokalen neurologischen Defiziten, sowohl transitorischen als auch persistenten, wurde nach Rücksprache mit der Neurologie eine kraniale Bildgebung durchgeführt.

## Ergebnisse

Patienten, die mit VKA Antagonisten behandelt wurden, haben häufiger einen CHA2DS2-VASC-Wert >2 als Patienten mit NOAC (58% versus 42%, p<0.01). Ebenso zeigte sich bei Patienten mit einer Niereninsuffizienz eine höhere Behandlungsrate mit VKA als mit NOAC (12% vs. 7%, p<0.001)**.**

Insgesamt traten 37 (1.6%) thromboembolische Ereignisse auf, davon waren 23 transitorische ischämische Attacken. Das Gesamtrisiko für ein thromboembolisches Ereignis war signifikant höher bei Patienten, die mit VKA behandelt wurden, im Vergleich zu Patienten mit NOAC (21 versus 16 Prozeduren, 2.2% versus 1.2%, p=0.04). Insbesondere Schlaganfälle waren häufiger bei Patienten unter Phenprocoumon (1%) im Vergleich zu Patienten unter NOAC (0.3%, p=0.02). Auch wenn NOAC vor der Katheterablation nicht pausiert wurde, kam es zu niedrigeren Raten thromboembolischer Ereignisse als mit Phenprocoumon (0.5% vs. 2.6%, p=0.05). Blutungskomplikationen nach der Ablation traten in beiden Gruppen gleich häufig auf (VKA n 122,13% vs. NOAC n 163, 12,6%). Es zeigte sich ebenfalls kein Unterschied zwischen den beiden Gruppen in Bezug auf leichte Blutungen, nicht schwere aber klinisch relevante Blutungen, sowie schwere Blutungen. Zusammenfassend traten nur sehr wenige (6%) schwere Blutungen auf, die meisten Blutungen waren leicht (n 206, 72%). Alter und HAS-BLED Score hatten keinen Einfluss auf das thromboembolische Risiko. Das Pausieren von OAC vor der Katheterablation steigerte signifikant das thromboembolische Risiko (OR 2.1, p=0.013). In beiden Gruppen war das Blutungsrisiko erhöht, wenn die orale Antikoagulation pausiert wurde mit OR 2.4 (Phenprocoumon 9% versus 21%, NOAC 7% versus 18%, p=0.07). Eine Unterbrechung der Therapie mit NOAC zeigte ein Anstieg des Blutungsrisikos von OR 2.3 (p=0.001).

## Schlussfolgerungen

Im Vergleich zu Phenprocoumon ist die Antikoagulation mit NOAC mit einem niedrigeren thromboembolischen Risiko assoziiert. In beiden Gruppen treten ähnliche Blutungskomplikationen auf. Um das Blutungsrisiko und Thromboembolie Risiko zu reduzieren, wäre eine ununterbrochene Therapie mit OAC zu bevorzugen.

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# 7 DECLARATION OF CONTRIBUTIONS

The dissertation work was carried out at the Herz-Zentrum Bodensee under the supervision of Prof.Dr.Volker Kühlkamp.

The study was designed in collaboration with Prof.Dr. Volker Kühlkamp, chief of department of electrophysiology.

Statistical analysis was carried out after a consultation with the Institute for

Biometry of the university of Tübingen by myself.

I confirm that I wrote the manuscript myself under the supervision of Prof.Dr.Volker Kühlkamp and that any additional sources of information have been duly cited.

# 8 ABBREVIATIONS

ACT→ active clotting time
AF→ atrial fibrillation
BMI→ body mass index
CCT→ cranial computed tomography
CT→ computed tomography
DC→ direct current
ECG→ electrocardiography
ESC→ European Society of Cardiology
GFR→ glomerular filtration rate
HR→ hazard ratio
INR→ international normalized ratio
ISTH→ International Society of Thrombosis and Haemostasis
LMWH→ low molecular-weight Heparin
MRI→ magnetic resonance imaging
NMCR→ non-major clinically relevant
NYHA→ New York Heart Association
NOAC→ novel oral anticoagulation
OAC→ oral anticoagulation
OR→ odds ratio
Phen. → Phenprocoumon
PVI→ pulmonary vein isolation
RF-Ablation→ radiofrequency ablation
RR→ relative risk
TEE→ transesophageal echocardiography
TIA→ transient ischemic attack
SEC→ spontaneous echo contrast
UFH→ unfractionated Heparin
VKA→ vitamin K antagonist

## Acknowledgements

I would like to thank my supervisor, Prof.Dr. Kühlkamp for inspiring me to begin with this work and to continue my activity as a researcher. I want to thank you for the insightful feedback and suggestions as well as the continuous support.

I am also very thankful for your guidance through the first years of my career in Germany as a young cardiologist and most of all thank you for making me discover and so much admire electrophysiology in specific. Thanks to your support and guidance I managed to bring my work in general to a higher level.