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A single center long-term comparison of remote magnetic navigation-assisted catheter ablation versus manual catheter ablation of atrial fibrillation

INAUGURAL-DISSERTATION

zur Erlangung des Doktorgrades
der Medizinischen Fakultät der
Georg-August-Universität zu Göttingen

vorgelegt von

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aus

Győr (Ungarn)

Göttingen 2023

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Datum der mündlichen Prüfung:	18.12.2024

Hiermit erkläre ich, die Dissertation mit dem Titel „A single center long-term comparison of remote magnetic navigation-assisted catheter ablation versus manual catheter ablation of atrial fibrillation“ eigenständig angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben.

Göttingen, den 10.12.2023 ……

(Unterschrift)

Die Daten, auf denen die vorliegende Arbeit basiert, wurden teilweise publiziert:

Schlögl S, Schlögl K, Haarmann H, Bengel P, Bergau L, Rasenack E, Hasenfuss G, Zabel M. (2022): Remote magnetic navigation versus manual catheter ablation of atrial fibrillation: A single center long-term comparison. Pacing Clin Electrophysiol 1,14-2

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3D	Three-dimensional
AADs	Antiarrhythmic drugs
ACT	Activated clotting time
AF	Atrial fibrillation
AT	Atrial tachycardie
AV	Atrioventricular
BMI	Body mass index
CAD	Coronary artery disease
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
DM	Diabetes mellitus
ECG	Electrocardiogram
EHRA	European Heart Rhythm Association
FU	Follow up
HR	Hazard ratio
IQR	Interquartile range
LA	Left atrial
LAA	Left atrial appendage
LIPV	Left inferior pulmonary vein
LSPV	Left superior pulmonary vein
LV	Left ventricular
MCN	Manual catheter navigation
MRI	Magnetic Resonance Imaging
OSA	Obstructive sleep apnea
QoL	Quality of life
RF	Radiofrequency
RMN	Remote magnetic navigation
PV	Pulmonary vein
PVI	Pulmonary vein isolation
RIPV	Right inferior pulmonary vein
RSPV	Right superior pulmonary vein
SD	Standard deviation
TIA	Transient ischemic attack
TsP	Transseptal puncture

1 Introduction

1.1 Definition of atrial fibrillation

Atrial fibrillation (AF) is a supraventricular arrhythmia characterized by the chaotic electrical activation of the atria, resulting in an uncoordinated atrial electrical activation and consequently ineffective atrial contraction (Hindricks et al. 2021).

1.2 Epidemiology of AF

AF leads to substantial difficulties for patients, physicians, and healthcare systems globally (Hindricks et al. 2021). Worldwide, AF is the most prevalent sustained cardiac arrhythmia in adults and affects around two to four percent of the population (Benjamin et al. 2019). In the future, a further 2.3-fold rise is expected because of the aging population and better diagnostic possibilities (Chugh et al. 2014; Krijthe et al. 2013). According to the Framingham Heart Study, a quarter of the population in the USA develops AF in their lifetime (Lloyd-Jones et al. 2004), which was found to be almost equivalent in the European population (Ricci et al. 2018). Later, it was estimated that these numbers would be even greater, putting the lifetime risk to 33% in a progressively aging European population (Magnussen et al. 2017; Staerk et al. 2018). Currently around 1.8 million Germans are affected by AF with the outlook of a further increasing prevalence of this disease (Kip et al. 2015).

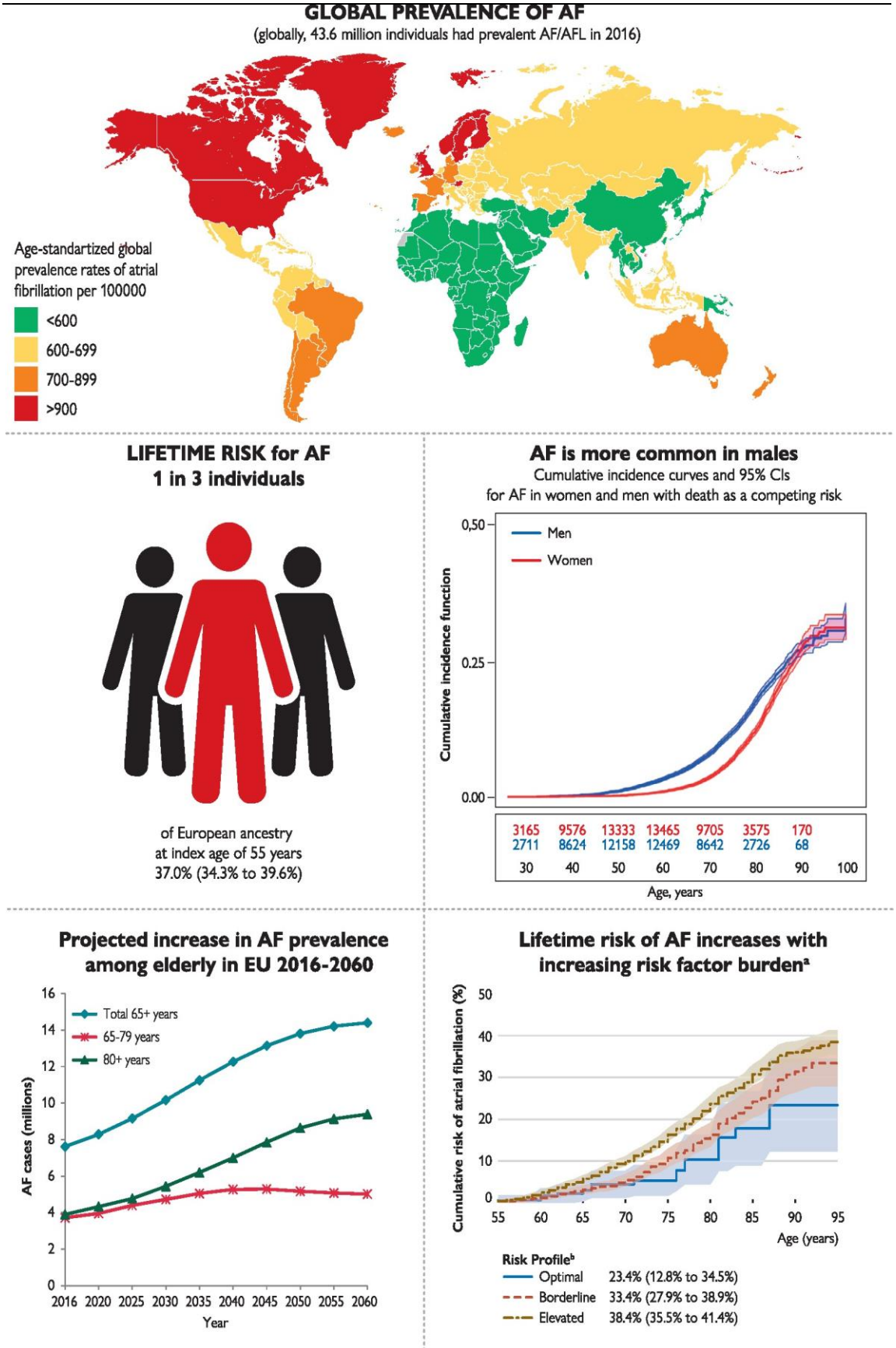

Figure 1: Prevalence and risk of AF (Hindricks et al. 2021) (upper panel), and lifetime risk and projected rise in the incidence and prevalence (lower panel). Reproduced with the permission of Oxford University Press.

1.3 Risk factors of AF

The risk factors of AF are well defined and identified in the literature (Hindricks et al. 2021). Non-modifiable risk factors consist of age (Staerk et al. 2018), sex (Magnussen et al. 2017), genetic predisposition (Hobbelt et al. 2017) and Caucasian heritage (Dewland et al. 2013). Modifiable risk factors are hypertension (Lip et al. 2017a), diabetes mellitus (DM) (Aune et al. 2018a), heart failure (HF) (Santhanakrishnan et al. 2016), coronary artery disease (CAD) (Michniewicz et al. 2018), alcohol consumption (Gallagher et al. 2017), smoking (Aune et al. 2018b), physical activity (Kwok et al. 2014), obesity (Nalliah et al. 2018), chronic kidney disease (CKD) (Boriani et al. 2015), obstructive sleep apnea (OSA) (Tung et al. 2017) and chronic obstructive pulmonary disease (COPD) (Desai et al. 2019). The modifiable risk factors are powerful drivers of AF evolution and progression and optimal targets of intervention in AF prevention (Hindricks et al. 2021).

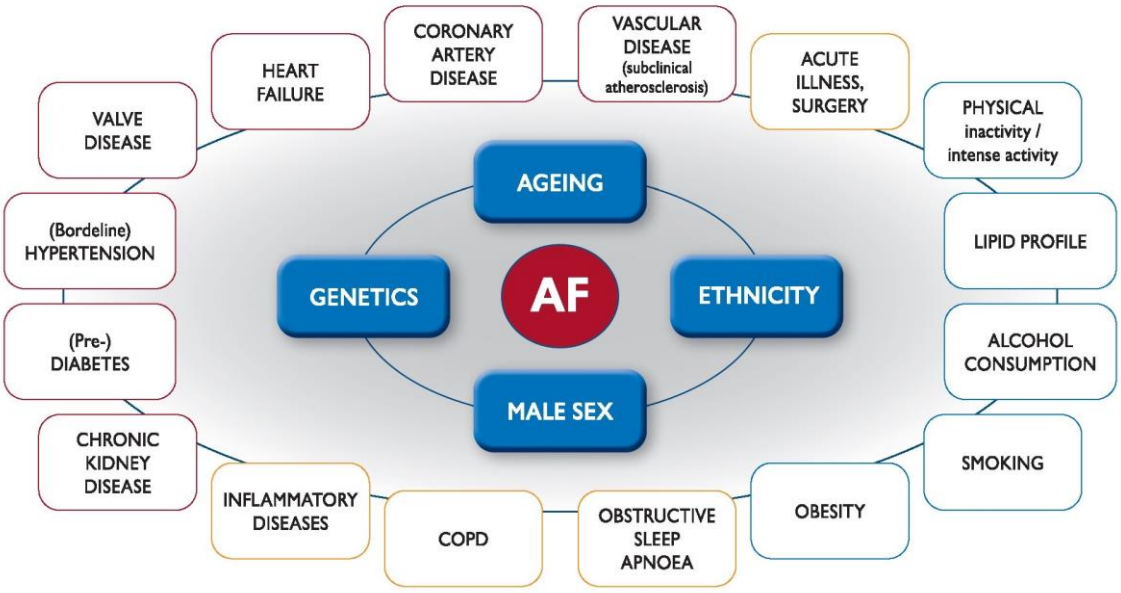

Figure 2: Review of risk factors for AF (Hindricks et al. 2021). Reproduced with the permission of Oxford University Press.

1.4 Clinical characteristics of AF

AF can be asymptomatic or symptomatic in clinical existence. In case of symptomatic AF, the most prevalent symptoms are palpitations, dyspnea, fatigue, chest pain, dizziness, and sleep disorders (Hindricks et al. 2021). As a fulminant manifestation, AF can induce hemodynamically unstable conditions leading to immediate life threat such as symptomatic hypotension, syncope, pulmonary oedema, acute HF, myocardial ischemia, or cardiogenic shock (Hindricks et al. 2021). To better classify the typical symptom burden of AF patients, the European Heart Rhythm Association (EHRA) proposed the EHRA-Classification (Wynn et al. 2014).

EHRA Staging	***Symptom burden***	***Definition***
EHRA I	No symptoms	Normal daily activity is possible
EHRA II	Mild Symptoms	
EHRA III	Heavy Symptoms	Normal daily activity is reduced
EHRA IV	Severe Symptoms	Normal daily activity is not possible

Table 1: EHRA symptom scale (Hindricks et al. 2021). Reproduced with the permission of Oxford University Press.

1.5 Common AF-related clinical outcomes

The most serious consequence of lasting AF is the persisting impact on everyday life of the patients and the clinical outcomes linked to the disease burden (Hindricks et al. 2021).

1.5.1 Cardioembolic stroke

The most common AF-related clinical fallout is cardioembolic stroke (Hindricks et al. 2021). Cardioembolic strokes linked to AF are usually serious, highly recurrent, often fatal, or with enduring disability (Benjamin et al. 2019). Yearly AF-related stroke risk in the AF population is subject to comorbidities (Olesen et al. 2011).

1.5.2 Left ventricular dysfunction

Left ventricular (LV) dysfunction and HF are well-studied repercussions of AF: multiple AF-related processes induce negative remodeling (Wijesurendra and Casadei 2015), resulting in a high prevalence and incidence of HF (Hindricks et al. 2021). AF and HF often coexist and beget each other because of shared risk factors and pathogenesis, leading to increased mortality compared to either condition alone (Ziff et al. 2018).

1.5.3 Cognitive impairment

AF may lead to cognitive impairment via clinically apparent pathways, silent stroke or until to this day insufficiently understood stroke-independent pathogenesis (Hindricks et al. 2021). Studies conducted with magnetic resonance imaging demonstrated a two-fold rise in the chances of developing silent cerebral ischemia due to AF (Dagres et al. 2018).

1.5.4 Hospitalization

A commonplace consequence of AF is recurrent hospitalization (Hindricks et al. 2021). Roughly one third of AF patients have at least one, and every tenth have more than two hospital admissions annually (Kirchhof et al. 2014), bringing the hospitalization risk twice as high as age- and sex-matched non-AF individuals (Kim et al. 2011).

1.5.5 Quality of life

The quality of life (QoL) is frequently significantly limited in AF patients (Hindricks et al. 2021). Almost two third of AF subjects have highly reduced QoL and exercise tolerance (Freeman et al. 2015). The frequency of anxiety disorders is also higher in AF patients (Serpytis et al. 2018).

1.5.6 Increased mortality

An et al. (2018) showed that the usual causes of death by AF patients were HF (14.5%), malignancy (23.1%) and infection/sepsis (17.3%), however stroke-related mortality was only 6.5%. A further study showed that mortality is independently associated with AF and leads to an overall 3.5 times rise in the risk of mortality (Magnussen et al. 2017).

1.6 Classification of AF

The classification of AF has been revised numerously, most recently in the actual EHRA Guidelines (Hindricks et al. 2021). It was necessary to develop a categorization, which could be used in the common clinical praxis. As a result, AF is currently categorized in five groups according to the presentation, duration, and spontaneous termination of the episodes (Hindricks et al. 2021).

AF pattern	***Definition***
First Diagnosed	AF not diagnosed before
Paroxysmal	AF terminating spontaneously or with intervention in 7 days of onset.
Persistent	AF continuously sustaining beyond 7 days, including episodes terminated by cardioversion (CV) after ≥7 days
Long-standing persistent	Continuous AF of >12 months' duration when decided to adopt a rhythm control strategy.
Permanent	AF when no attempts will be undertaken to restore sinus rhythm

Table 2: AF classification (Hindricks et al. 2021). Reproduced with the permission of Oxford University Press.

1.7 Diagnosis of AF

There have been several methods developed to diagnose AF effectively on a mass scale; however, the gold standard is a 12-lead-Electrocardiogram (ECG) to this very day (Steinberg et al. 2018). The sensitivity and specificity of the most common methods are summarized in Table 3 compared to 12-lead-ECG (Mairesse et al. 2017). The diagnostic criterion of AF is a at least 30 seconds long episode of on a rhythm strip or 5 minutes by implanted cardiac devices if AF documented (Hindricks et al. 2021).

Diagnostic tools	*Sensitivity*	*Specificity*
Pulse taking	87 – 97%	70 – 81%
Blood pressure monitors	93 – 100%	86 – 92%
Single lead ECG	94 – 98%	76 – 95%
Smartphone apps	91 – 98%	91 – 100%
Watches	97 – 99%	83 – 94%

Table 3: Screening tools in AF (Hindricks et al. 2021). Reproduced with the permission of Oxford University Press.

1.8 Treatment of AF

The current EHRA guideline (Hindricks et al. 2021) underline the integration of a holistic treatment approach, the so-called ABC pathway (Lip 2017b). In comparison to usual care, the use of the ABC pathway has been associated with lower risk of all-cause death and a composite outcome of stroke, major bleeding, cardiovascular death and first hospitalization (Proietti et al. 2018).

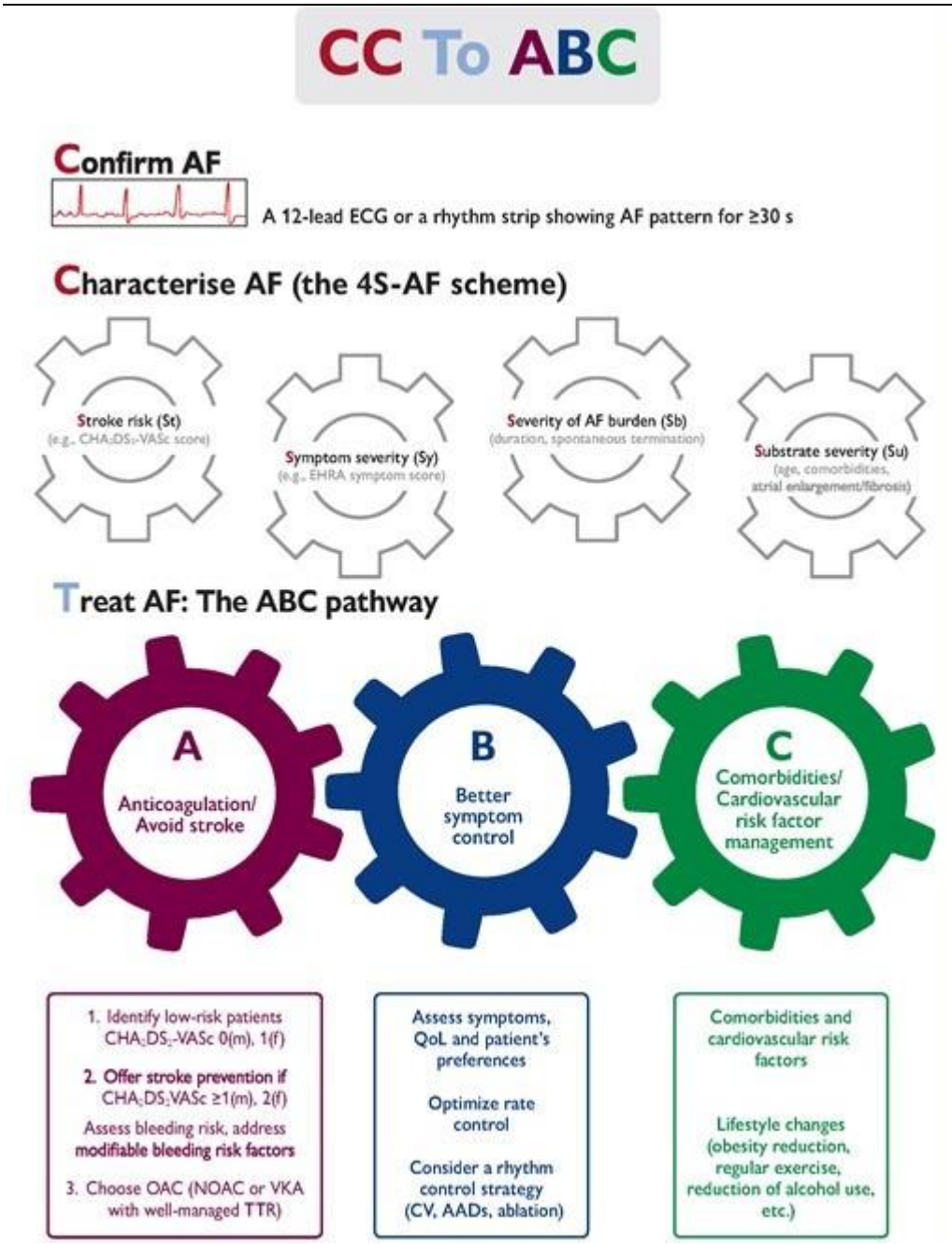

Figure 3: CC to ABC: effective management of AF (Lip 2017b, Hindricks et al. 2021). Reproduced with the permission of Oxford University Press.

1.8.1 Letter 'A' – Avoid stroke

The cornerstone of effective AF therapy is the management of the thromboembolic risk (Hindricks et al. 2021). In general, the risk of stroke is five times higher under AF; however, this risk is not uniform, mainly depending on the presence of specific stroke risk factors/modifiers (Lip et al. 2010). As a result, Lip et al. (2010) developed the CHA_2DS_2-VASc [Congestive HF, Hypertension, Age ≥75 years, DM, Stroke, Vascular disease, Age 65–74 years, Sex category (female)] score to evaluate the clinical stroke risk from the universally known risk factors.

CHA_2DS_2-VASc score

	Risk factors	***Points***	***Definition***
C	**Congestive heart failure**	1	Clinical HF or moderate to severe LV dysfunction, or hypertrophic cardiomyopathy
H	**Hypertension**	1	Clinical Hypertension or an antihypertensive therapy
A_1	**Age 75 years or older**	1	Age 75 years or older
D	**Diabetes mellitus**	1	Treatment with oral hypoglycaemic drugs and/or insulin or fasting blood glucose >125 mg/dL (7 mmol/L)
S_2	**Stroke**	2	Previous stroke, TIA, or thromboembolism
V	**Vascular disease**	1	Angiographically significant CAD, previous myocardial infarction, PAD, or aortic plaque
A_2	**Age 65 − 74 years**	1	Age 65 − 74 years
Sc	**Sex category (female)**	1	Sex category (female)

Table 4: The CHA_2DS_2-VASc Score (Lip et al. 2010; Hindricks et al. 2021). Reproduced with the permission of Oxford University Press.

CHA_2DS_2-VASc performs only modestly in predicting accurately high-risk patients who will develop thrombo-embolic events. However, those detected as low-risk [CHA_2DS_2-VASc 0 (males), or score of 1 (females)] always had in the previous studies a low ischemic stroke or mortality rate (<1%/year) and as a result do not have the medical indication to any stroke prevention treatment (Hindricks et al. 2021). To better assess bleeding risk under anticoagulants by atrial fibrillation, the HAS-BLED Score was developed (Pisters et al. 2010). This score system summarizes seven clinically relevant factors (Table 5) leading to increased risk of bleeding (defined as 1-year risk for major intracranial bleeding, hospitalization as a result of bleeding, hemoglobin decrease >2 g/L, and/or transfusion) (Pisters et al. 2010).

HAS-BLED score

	Risk factors	***Points***	***Definition***
H	**Hypertension**	1	Clinical hypertension or an antihypertensive therapy

A	**Abnormal renal/liver function (1 point each)**	1 or 2	Presence of chronic dialysis, renal transplantation, or serum creatinine≥200 mmol/L, chronic hepatic disease (cirrhosis) or biochemical evidence of significant hepatic derangement (bilirubin x2 in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase x3 upper limit of normal)
S	**Stroke**	1	Previous hemorrhagic stroke
B	**Bleeding**	1	Previous bleeding
L	**Labile INR value**	1	Therapeutic time in range<60%
E	**Elderly**	1	Age≥65 years
D	**Drugs/Alcohol (1 point each)**	1 or 2	Antiplatelet agents, nonsteroidal anti-inflammatory drugs. ≥8 units alcoholic consumption per week

Table 5: The HAS-BLED Score

1.8.2 Letter 'B' – Better symptom control

The second main point of AF management is symptom control, which is based on the EHRA symptom Score (Wynn et al. 2014). We can characterize two main management strategies:

1.8.2.1 Rate control

Rate control involves the use of negatively chronotropic drugs or electrophysiological/surgical interventions to reduce the rapid ventricular rate often found in patients with AF (Camm et al. 2007). Despite of losing importance lately, rate control plays a crucial part of AF management (Hindricks et al. 2021). The most important drugs and their features used in rate control were summarized according to Hindrick et al. (2021) in Table 6. The target of the pharmacological rate control is the slowing of atrioventricular (AV) conduction ensuing a 60 to 80 bpm in resting and 90 to 115 bpm under physical activity (Fuster et al. 2011). The current EHRA guideline recommends a rate control only after a futile attempt of rhythm control (Hindricks et al. 2021)

	Intravenous administration	***Maintenance dose***	***Contraindicated***
Beta-blockers			
Metoprolol tartrate	2.5 − 5 mg i.v. bolus; up to 4 doses	25 − 100 mg	Contraindicated in acute HF, asthma and severe bronchospasm
Metoprolol succinate	N/A	50 − 400 mg	
Bisoprolol	N/A	1.25 − 20 mg	

Atenolol	N/A	25 – 100 mg	
Esmolol	500 μg/kg i.v. bolus over 1 min; followed by 50 – 300 μg/kg/min	-	
Landiolol	100 μg/kg i.v. bolus over 1 min, followed by 10 - 40 μg/kg/min; in patients with cardiac dysfunction: 1 - 10 μg/kg/min	-	
Nebivolol	N/A	2.5 – 10 mg	
Carvedilol	N/A	3.125 – 50 mg	
Non-dihydropyridine calcium channel antagonists			
Verapamil	2.5 – 10 mg i.v. bolus over 5 min	40- 480 mg	Avoid in severe HF
Diltiazem	0.25 mg/kg i.v. bolus over 5 min, then 5 – 15 mg/h	60-360 mg	
Digitalis glycosides			
Digoxin	0.5 mg i.v. bolus (0.75 – 1.5 mg over 24 hours in divided doses)	0.0625 – 0.25 mg	Higher mortality by increased plasma dose. Dose in CKD patients should be adapted
Digitoxin	0.4 – 0.6 mg	0.05 – 0.1 mg	Increased mortality by high plasma dose

Table 6: Rate control with drugs in AF (Hindricks et al. 2021). Reproduced with the permission of Oxford University Press.

A special field of rate control is the so-called pace and ablate strategy. This consists of AV node ablation and pacing with a cardiac device (Hindricks et al. 2021). This method is seen as a last resort when medication fails. However, according to Lim et al. (2007) the pace and ablate strategy is associated with comparable complication rates and decreased long-term mortality risk compared to the standard pharmacological rate control. AV node ablation combined with cardiac resynchronization therapy is even favored in symptomatic patients with permanent AF and at least one hospitalization for HF (Brignole et al. 2018). As the possibilities in physiological pacing expand, physiological pacing after AV node ablation may evolve as an attractive pacing modality (Huang et al. 2018).

1.8.2.2 Rhythm control

The rhythm control strategy refers to the strategy, where the main goal is the restoration and maintenance of sinus rhythm (Hindricks et al. 2021). This strategy incorporates several treatment modalities, including CV, antiarrhythmic drugs (AADs) and catheter ablation (Hindricks et al. 2021). As Zhang et al (2013) reported, AF progression was significantly decreased as a result of rhythm control compared to rate control. Lately, early rhythm-control

therapy was associated with a lower risk of adverse cardiovascular outcomes than usual care among patients with early AF and cardiovascular conditions, thus showing the possible superiority compared to other therapeutic approaches (Kirchhof et al. 2020). According to Dan et al. (2018) and Hindricks et al. (2021), we summarized the frequently used AADs in rhythm control in Table 7.

Antiarrhythmic drugs for restoration of sinus rhythm (pharmacological cardioversion)

Drug	Administration	Initial dose	Further dosing	Success rate	Comments
Flecainide	Oral, i.v.	200 - 300 mg 2 mg/kg over 10 min	–	Overall: 59–78%	Contraindicated by structural heart disease and ischemic etiology and cardioversion by atrial flutter. Can lead to hypotension, AFL with 1:1 conduction, widening of the QRS complex.
Propafenone	Oral, i.v.	450–600 mg 1.5 – 2 mg /kg over 10 min	–	Oral: 45–78%; i.v.: 43–89%	
Vernakalant	i.v.	3 mg/kg over 10 min	2 mg/kg over 10 min (10 – 15 min after the initial dose)	50% conversion within 10 min	Contraindicated by arterial hypotension, acute coronary syndrome, end stage HF, severe aortic stenosis and prolonged QT duration. May induce severe hypotension, prolongation of QT, widening of the QRS complex and non-sustained ventricular tachycardia.
Amiodarone	i.v.	5 – 7 mg/kg over 1 – 2 h	50 mg/h (maximum 1.2 g for 24 h)	44%	Can lead bradycardia/severe AV block, QT prolongation, hyperthyroidism, lung fibrosis, light sensitivity, and corneal deposits. Contraindicated by hypothyroidism
Ibutilide	i.v.	1 mg over 10 min 0.01 mg/kg if body weight <60 kg	1 mg over 10 min (10 – 20 min after the initial dose)	31–51% (AF) 63–73% (atrial flutter)	Effective for conversion of atrial flutter. Contraindicated by prolonged QT, severe LV hypertrophy and reduced LV ejection function. Can lead to QT prolongation and torsade des pointes tachycardia.

Table 7: Rhythm control with antiarrhythmic drugs (Hindricks et al. 2021). Reproduced with the permission of Oxford University Press.

1.9 Catheter ablation of AF

Catheter ablation is a well-established treatment for the prevention of AF recurrences (Arbelo et al. 2017). The main clinical benefit of AF catheter ablation is the reduction of arrhythmia-related symptoms (Mark et al. 2019). Furthermore, selected patients like HF patients (Marrouche et al. 2018) benefit even more from catheter ablation in form of reduced mortality and rate of hospitalization. Recent studies showed also that catheter ablation is superior compared to AADs in terms of efficacy and QoL (Packer et al. 2019). Despite of these findings, ablation is recommended, in general, as a second-line therapy after failure (or intolerance) of AADs (Hindricks et al. 2021).

1.9.1 History of catheter ablation

The first catheter ablation in humans was performed by Scheinman et al. (1982). 17 years later, Haïssaguerre et al. (1998) were the first to discover the importance of arrhythmogenic foci in the pulmonary veins (PVs) as initiator of AF. As a therapeutic solution, an approach was developed to address these foci with the use of catheter ablation (Haïssaguerre et al. 1998). However, the selective ablation of these foci was complicated. Furthermore, the risk of developing complications, especially a PV stenosis was high (Gerstenfeld et al. 2001). Pappone et al. (2000) improved this approach by doing a circumferential ablation line around the PVs: instead of approaching the challenge of the PVs with separate ablation lesions, he combined the ablation points in the antrum of the PVs into a continuous circumferential line around the PV antrum. As a result, the PVs were electrically separated from the left atrium. Furthermore, the risk of a PV stenosis was significantly reduced (Pappone et al. 2000). As a result of this discovery the circumferential isolation of PVs became the standard approach to AF catheter ablation, either using point-by-point radiofrequency (RF) ablation or single-shot ablation devices (Jaïs et al. 2008; Packer et al. 2013; Dukkipati et al. 2015; Reddy et al. 2015; Sohara et al. 2016; Bradley and Haines 2020).

1.9.2 Three-dimensional electroanatomic mapping

To enhance the navigation in the left atrium and to visualize and aid the complete isolation of the PVs the three-dimensional (3D) electroanatomic mapping was developed (Gepstein et al. 1997). Through the real-time reconstruction of the PV anatomy, the surgeon is able to navigate real time in the left atria. (Figure 4).

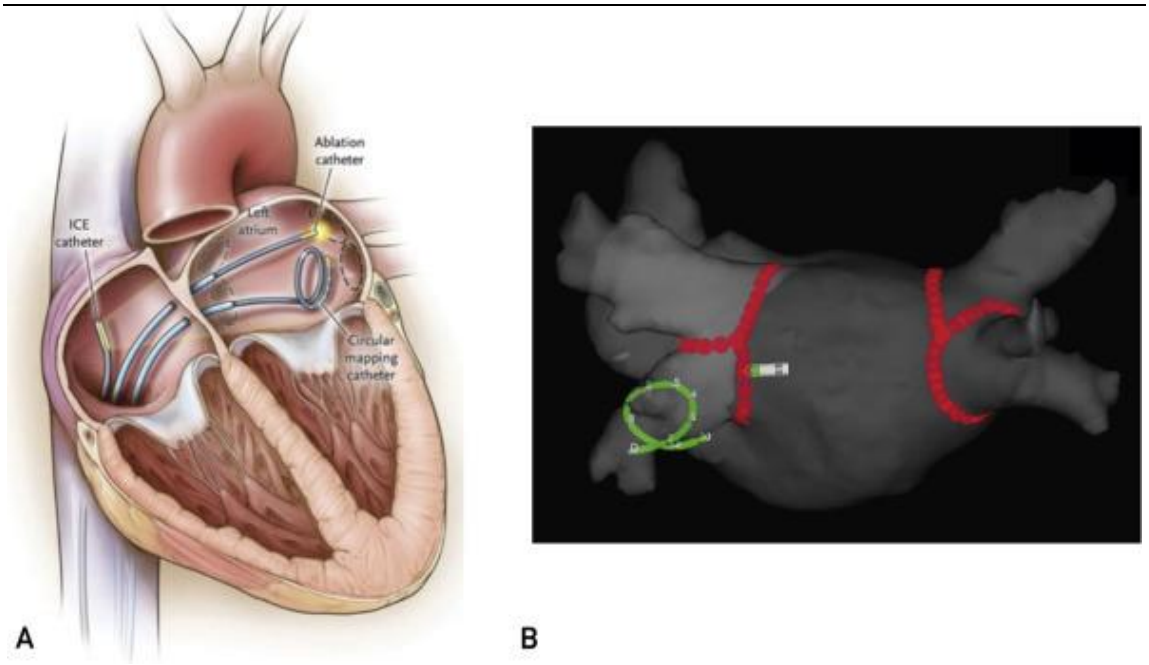

Figure 4: Pulmonary vein isolation using a standard radiofrequency catheter. A: figure depicting PVI, B: 3D map of the atrium with ablation points around the PVs (Morin et al 2016). Reproduced with the permission of Elsevier.

Later, these systems improved to include the merging of real-time anatomy with previously performed computertomographie (CT)-scans of the heart (Caponi et al. 2010), also allowing features like displaying the values of contact force (CF) between the ablation catheter and cardiac tissue on the navigation map itself (Bertagnolli et al. 2018). Nowadays the use of 3D electroanatomic mapping system became the cornerstone of efficient and safe PV isolation (PVI) (Calkins et al. 2018).

1.9.3 Possible PVI complications

PVI is a widely adopted and safe interventional approach because of constant technological and safety innovations (Calkins et al. 2018). However, as this approach is potentially lethal in untrained hands and has risks even by veteran electrophysiologists. It was crucial to characterize the most important complications. Cappato et al. (2005 and 2010) published two worldwide surveys describing the complication profile of PVI. In the first survey in 2005, the cumulative complication rate stood at 5.9%. Later in the repeated survey in 2010, 4.5% of the procedures were linked with a complication. The most important complications are:

1.9.3.1 Cardiac tamponade

Cardiac tamponade is the most common life-threatening complication associated with PVI (Deshmukh et al. 2013). According to the Cappato et al. (2010), it was present in 1.3% of the cases. There are three main causes of cardiac perforation leading to cardiac tamponade according to Calkins et al. (2018). First, poorly performed transseptal puncture (TsP) can lead to a mechanical trauma causing bleeding and consequent tamponade. Second, direct

mechanical perforation with the tools used during the PVI could also cause a bleeding, especially in the area of the left atrial appendage (LAA). Lastly, during the delivery of the RF energy there is a risk of overheating leading to a steam pop and a possible mechanical trauma to the atrial wall, leading to perforation. Uncontrolled use of ablation power, temperatures, and catheter CF also plays an important role in this complication (Calkins et al. 2018). Importantly, the risk of developing a cardiac tamponade is almost twice as high by women (Calkins et al. 2018), probably due to anatomical reasons. The experience of the operator is essential. It was observed that there is a reciprocal relationship between center and operator volume of PVI procedures and the prevalence of cardiac tamponade (Calkins et al. 2018), therefore rigorous training is mandatory. Cardiac tamponade presents either as a sudden collapse of blood pressure or deceptively, as a progressive decline (Calkins et al. 2018). It is key, that the interventional team be vigilant and trained to the development of cardiac tamponade, as a delay in diagnosis and treatment can be fatal (Calkins et al. 2018). Hypotension by any patient undergoing PVI should be seen a sign of a tamponade until proven otherwise (Calkins et al. 2018). However, it is important to point out, that minor, asymptomatic pericardial effusions are also common after PVI (Calkins et al. 2018). Cardiac tamponade can be solved mostly with immediate percutaneous drainage (Calkins et al. 2018). In rare cases, surgical drainage and repair could be necessary (Bunch et al. 2005). According to Michowitz et al (2014), 16% of the cases with cardiac tamponade needed a surgical intervention. As a direct result, PVI procedures should only be allowed in experienced hospitals equipped and prepared to handle these emergencies (Calkins et al. 2018).

1.9.3.2 Cerebrovascular thromboembolic event

The latest survey reports about 0.9% of the cases with a cerebrovascular event (Cappato et al. 2010), either presenting as a stroke or a transient ischemic attack (TIA). The overwhelming number of these events take place within 48 hours after the PVI and usually do not cause a lasting disability if competently managed (Scherr et al. 2009; Patel et al. 2010). There are several explanations proposed as a potential pathogenesis of these events. Firstly, the accumulation of thrombi on the venous sheaths (Ren et al. 2004) or directly at the site of ablation lesions can lead to a thromboembolic event. Secondly, regardless of a high natural closure percentage, TsP may lead to a lasting atrial septal defect, leaving the possibility for paradoxical embolism (Rillig et al. 2010). Thirdly, the iatrogenic suction of air during the procedure could also cause an air embolism (Hinkle et al. 2001). Lastly, as a rarity, a highly damaged LA diastolic dysfunction (stiff LA syndrome) is present in around 1% of post PVI patients, causing thromboembolism (Gibson et al. 2011). The prevalence of thromboembolic complications can be effectively lowered with a combination of thorough periprocedural imaging, meticulous anticoagulation, strict sheath management, and careful control of RF delivery (Calkins et al. 2018). The diagnosis of these events is usually straightforward with radiological imaging. However, it is important to note, that there is diagnostic postponement of these events during PVI because of general anesthesia (Calkins et al. 2018). The treatment

of these events is heavily depending on the anatomical region. A surgical thrombectomy is a possible solution, however mainly by peripheral arterial embolization, as cerebral embolization is usually managed conservatively (Calkins et al. 2018). There have been also new surgical avenues opened with the advance of percutaneous interventional techniques (Calkins et al. 2018).

1.9.3.3 Vascular complications

Complications of the vascular access are the most frequent complications of PVI (Calkins et al. 2018). These events include groin hematoma, retroperitoneal bleeding, femoral artery pseudoaneurysm, or arteriovenous fistula (Calkins et al. 2018). Cappato et al. (2010) reports these complications to be present by 1.5% of the patients undergoing PVI. Most of these complications can be effectively dealt with conservatively (Calkins et al. 2018). However, vascular events such as pseudoaneurysm, arteriovenous fistula and retroperitoneal bleeding might require blood transfusion and/or surgical intervention, increasing morbidity and hospitalization (Waigand et al. 1999). Effective prevention of these complications is the real-time ultrasound-guided puncture of the femoral veins. According to Tanaka-Esposito et al. (2013), ultrasound guidance reduces significantly both major and minor vascular events by PVI.

1.9.3.4 PV stenosis

Historically, PV stenosis is one of the earliest discovered complications (Haïssaguerre et al. 1998). The pathogenesis is linked to the thermal injury of the PVs on the level of media, intima, adventitia, musculature of the PV or combined (Calkins et al. 2018). This complication is present in 0.3% of the cases (Cappato et al. 2010). Usual clinical manifestation are progressive dyspnea, hemoptysis, cough, chronic pulmonary infections and chest pain, leading the clinician often to misdiagnosis and mistreatment (Calkins et al. 2018). The choice of diagnostics is mostly chest CT, Magnetic Resonance Imaging (MRI), perfusion scan, transesophageal echocardiography, or venography of the pulmonary veins (Calkins et al. 2018). The most sensitive and specific modalities are MRI and CT (Calkins et al. 2018). Edge of MRI is the availability of concurrent perfusion information and zero radiation (Calkins et al. 2018). Treatment of choice is minimally invasive stenting or balloon angioplasty (Qureshi et al. 2003). Recently, the number of this complication is decreasing because of wide antral PVI (Proietti et al. 2014). Nowadays, the prevalence of this complication is almost non-existent in experienced centers Calkins et al 2018).

1.9.3.5 Atrio-Esophageal fistula

An atrio-esophageal fistula is defined as a connection between the atrium and the lumen of the esophagus (Calkins et al. 2018). It occurs around 0.04% of the cases (Cappato et al. 2010). Pathogenesis of this complication is linked to thermal trauma to the esophagus

through the ablation lesions during the PVI. Common site of the ablation lesions leading to atriol-esophageal fistula is on the posterior wall, which is mostly occurring by the ablation of the right sided pulmonary veins or by linear lesions on the posterior wall (Cummings et al. 2005). The typical clinical course is dysphagia, hematemesis, sepsis or air embolism few days to even a month after the ablation (Calkins et al. 2018). Diagnosis is mostly based on the clinical symptoms, however, includes the documentation of esophageal erosion combined with evidence of a fistulous connection to the atrium (Calkins et al. 2018). The most useful and safe tool to an early diagnosis is contrast-enhanced CT scan or an MRI scan (Calkins et al. 2018). An atrio-esophageal fistula is an extremely rare complication; however, it is the most lethal (Pappone al. 2004). The only bail out therapy is the surgical extirpation of the esophagus (Yousuf et al. 2016). As the consequences of this complication are grave, the most useful tool is prevention. Reduced ablation power output on the posterior LA wall and the use of thermal probes are the best preventive strategies (Singh et al. 2008). Another commonplace prevention is the use of proton pump inhibitors. Although this approach is widely used, it has never been scientifically proven (Calkins et al. 2018).

1.9.3.6 Phrenic palsy

As both phrenic nerves are anatomically adjacent to the epicardia, they are prone to thermic damage during PVI (Calkins et al. 2018). This complication occurs in 0.2% of the cases (Cappato et al. 2010). Most commonly, the thermic damage is only transitory. In rare cases, however, permanent palsy with dyspnea, cough and reduced endurance could be provoked (Bai et al. 2006). The diagnostic modality is chest X-ray, which proves an elevated hemidiaphragm of the ipsilateral lung (Calkins et al. 2018). There have been several strategies developed to prevent this complication. First, limiting ablation on the antral regions can be preventive. Second, high-output pace mapping with tagging of phrenic capture before the ablation could identify dangerous anatomical regions. Third, palpation of diaphragmatic excursion during ablation is a preventive method. Lastly, fluoroscopic or intracardiac ultrasound guided imaging during pacing of the phrenic nerves could be helpful (Calkins et al. 2018). There is no selective treatment known to promote healing; however, if there is permanent nerve palsy with significant symptoms, diaphragmatic plication could ease symptom burden (Calkins et al. 2018).

1.9.4 Radiofrequency ablation with manual navigation

1.9.4.1 Pathophysiology of radiofrequency ablation

RF energy induces myocardial damage by producing direct heating of the adjacent tissue by means of successive heat transmission to the tissue beneath (Zipes et al. 2017). An inevitable coagulation necrosis can be achieved within seconds and with temperatures of 50 °C or higher leading to a myocardial scar and conduction block (Zipes et al. 2017). Six crucial aspects of RF ablation have been identified in the last two decades as decisive factors for

determining the extent of RF lesions, consequently the efficacy and safety of this method: power, impedance, temperature, duration, catheter stability and CF (Calkins et al. 2018).

1.9.4.2 Interplay between power, impedance, temperature, and application duration

The fundaments of effective lesion creation are ideal power delivery and solid electrode–tissue contact. The optimal duration of delivery time to enhance lesion formation is approximately 15–30 seconds, however, this time is largely depending on the power used; therefore, the ultimate lesion can be achieved practically around a minute (Calkins et al. 2018). If temperature exceeds 100 °C, clot and char could form on the tip of the ablation catheter. As char forms on the electrode, available ablation surface area decreases, in a positive feedback loop causing an abrupt upsurge in electrical impedance, thus causing steam pops or defective function of the ablation catheter (Calkins et al. 2018). To approach this complex issue, convective cooling was offered as a solution: elevated and safe power transmission can be either carried out using active cooling with saline-irrigation of the catheter tip or using a passive advancement of the conduction by deploying materials with excellent thermal conductivity like gold (Calkins et al. 2018). Therefore, PVI is usually executed nowadays with irrigated tip catheters (Thomas et al. 2004; Calkins et al. 2018). Materials such as gold did not become standard because of economical and efficacy reasons.

1.9.4.3 Contact force

A central factor in the optimal lesion creation is the CF exerted by the tip of the ablation catheter on the ablated tissue (Yokoyama et al. 2008). Insufficient CF leads to a rapid electrical reconnection whilst exaggerated CF can cause steam pops and pericardiac effusion as a result of cardiac perforation (Yokoyama et al. 2008). CF sensing catheters were introduced to maximize clinical efficacy and to better manage these risks (Kuck et al. 2012). Previous randomized and non-randomized studies show contradicting results comparting the efficacy of CF sensing and non-CF catheters, however most of the studies are showing a clinical benefit (Schlögl et al. 2022a).

1.9.4.4 Catheter stability

The backbone of catheter stability and therefore of successful PVI is accurate catheter maneuvering and stable catheter-tissue contact. Even the most experienced electrophysiologists occasionally experience difficulties maintaining stable contact (Pappone et al. 2006). This is specifically true for regions of complex anatomy where stability during maneuvering and ablation is crucial (Pappone et al. 2006). To tackle this challenge steerable sheaths were developed. The use of these sheaths helps the electrophysiologist to maintain better general maneuverability, leading to improved clinical efficacy and better periprocedural results (Piorkowski et al. 2011). The current generation of steerable sheaths allows real time visualization. The initial results show a significant improvement regarding

catheter stability, reduction of RF time and reduction of fluoroscopy without a bargain to safety or efficacy (Rajendra et al. 2023).

1.9.4.5 Drawbacks of manually guided ablation of atrial fibrillation

To understand the driving force behind remote magnetic navigation, we should first discuss the drawbacks of the manual guided approach.

1.9.4.5.1.1 Restricted freedom of movement

Manually maneuvered ablation catheters have several fundamental limitations. Catheter deflection can only take place with a certain radius restricted in only one plane limiting movement freedom (Faddis et al. 2002). Side-to-side catheter motion is executed by torque transmission which could be restricted through blood vessels tortuosity and the location of the ablation catheter inside the heart (Faddis et al. 2002).

1.9.4.5.1.2 Unstable tissue contact

Cardiopulmonary motion and failing catheter compliance can jeopardize stable catheter-tissue contact. These disadvantages are critical in case of complex arrhythmias like atrial fibrillation, as the creation of focal and linear lesions rely on accurate control of the catheter (Ernst et al. 2004).

1.9.4.5.1.3 Fluoroscopy burden

Fluoroscopy is an often-used technology in the field of medicine dating back to the 19th century. It is used regularly to guide invasive procedures; however, its use is linked to significant risks through ionizing radiation (Roguin et al. 2012). To address this issue, radiological protection was developed. Nonetheless, these protective measures have also been linked to substantial long-term orthopedic risks amongst electrophysiologist and interventional cardiologists (Goldstein et al. 2004).

1.9.5 Radiofrequency ablation using remote magnetic navigation

1.9.5.1 Remote magnetic navigation system

To overcome the above-mentioned drawbacks of manual navigation, remote magnetic navigation (RMN) was developed. The main features of the RMN system have been previously published (Ernst et al. 2004; Pappone et al. 2006). To summarize, the magnetic system relies on two focused-field permanent magnets of a neodymium-iron-boron compound that are controlled by a computer and are located on the side of the patient (Ernst et al. 2004). The magnetic field is able to create a 360° omnidirectional rotation of the catheter-tip and catheter by a uniform magnetic field (0.08 T) translating to an approximately spherical navigation volume of 20-cm diameter located inside the patient's chest. Magnetic

navigation complex is combined with a modified C-arm single-plane digital imaging system (Figure 4). The combination of rotation, translation, and tilt movements is possible without any limitation and adjusted by means of magnetic field in the spherical navigation volume. The operator is situated in the control room, at a distance from fluoroscopy and the patient's body (Pappone et al. 2006) (Figure 5).

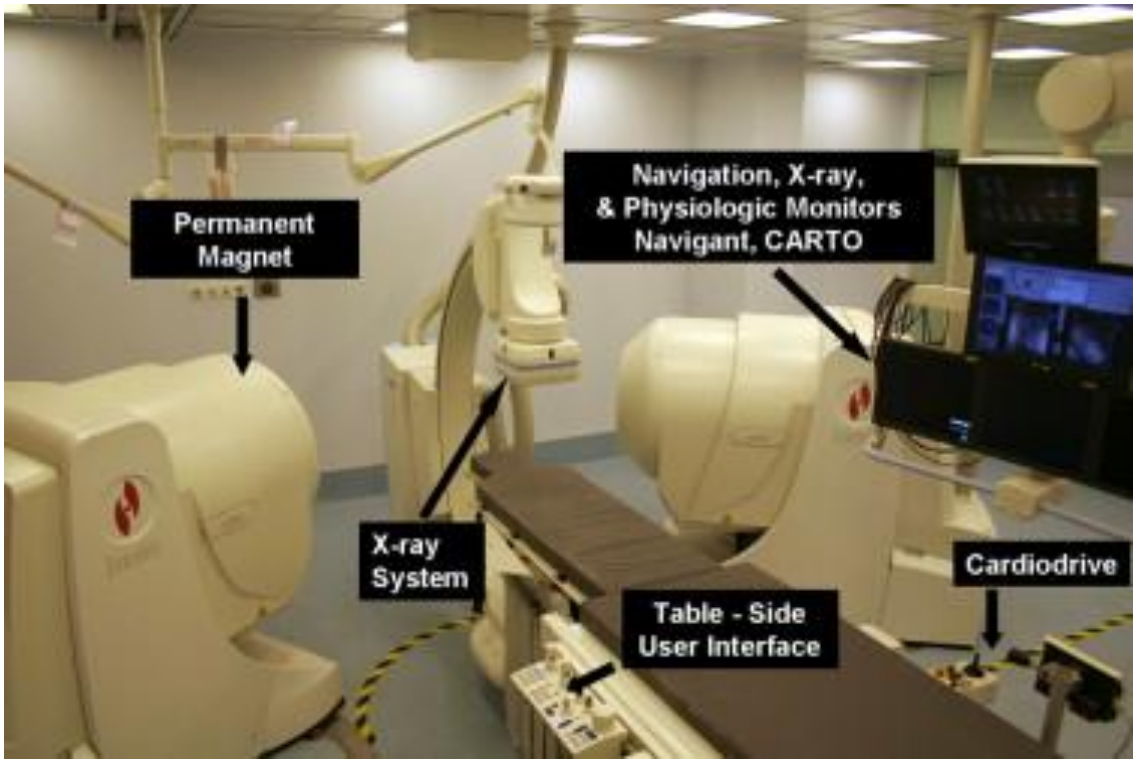

Figure 5: Remote magnetic navigation system (Latcu et al 2009). Reproduced with the permission of Elsevier Masson.

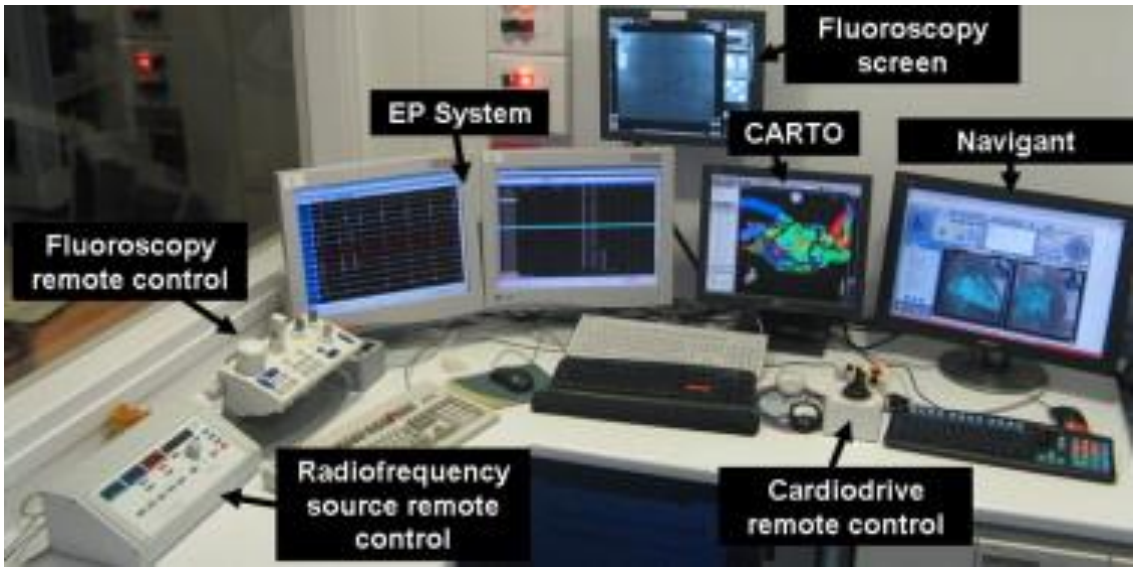

Figure 6: Control room of the remote magnetic navigation system (Latcu et al 2009). Reproduced with the permission of Elsevier Masson.

A 4-mm flexible catheter (NaviStar®-RMT, Biosense Webster, Diamond Bar, California) can be moved and steered with the incorporated small permanent magnets in the tip and in the distal segment of the catheter by the RMN system. The catheter can be advanced and retracted by a separate mechanism (Cardiodrive®, Stereotaxis Inc.; Figure 6). All of the magnetic vectors can be saved in the 3D magnetic sphere and reapplied with automatic navigation to the desired location. The user interface together with the magnetic device and the Cardiodrive® unit (Stereotaxis Inc.) allows an exact orientation change in 1° increments and longitudinal adjustments in 1-mm steps. For additional support, X-ray images can be transferred to the RMN to aid as an anatomical reference (Pappone et al. 2006).

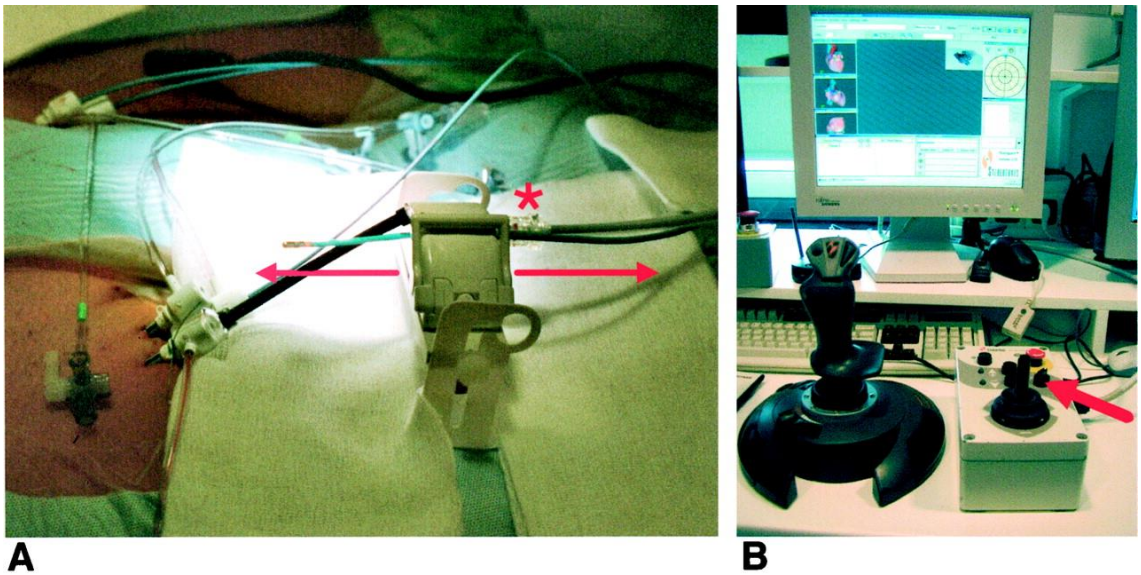

Figure 7: Cardiodrive® system and the navigation software. (Latcu et al 2009). Reproduced with the permission of Elsevier Masson.

The RMN platform is integrated with a 3D electroanatomic mapping system, the CARTO® RMT software (Stereotaxis Inc.). The CARTO® RMT software provides live catheter location and orientation to the RMN. It also provides further target locations, information about anatomical and ablation points and anatomical surface data from the electroanatomic map.

1.9.5.2 The role of RMN-guided ablation of atrial fibrillation

It was hypothesized that this method of navigation could provide the following benefits in comparison to the conventional manual approach:

1. Practically zero fluoroscopy time and dose to the personnel
2. Reduced fluoroscopy time and dose to the patient
3. Higher precision of navigation and ablation
4. Reduced complication rate

Most of the promises were fulfilled in previous studies (Virk et al. 2019). However, it is important to note, that regardless of everyday clinical use, a randomized multicenter controlled trial comparing RMN to manual catheter navigation (MCN) is still lacking to date. Clinical efficacy of RMN guided PVI was reported to be mostly non-inferior to MCN in previous retrospective studies (Pappone et al. 2006; Di Biase et al. 2007; Katsiyiannis et al. 2008; Miyazaki et al. 2010; Sorgente et al. 2010; Arya et al. 2011; Choi et al. 2011; Solheim et al. 2011; Adragão et al. 2016; Weiss et al. 2016; Kataria et al. 2017; Yuan et al. 2017; Jez et al. 2020) including initial prospective results from our center (Lüthje et al. 2011). However, most of these studies enrolled only a small number of patients with limited follow up, mainly with paroxysmal atrial fibrillation. The long-term clinical efficacy of RMN guided ablation in persistent AF has been already debated however not proven (Koutalas et al. 2015; Virk et al. 2019).

1.10 Aims

The main purpose of our study was to compare the long-term clinical efficacy of RMN guided PVI to the standard MCN approach. Secondary aim was to analyze procedural characteristics and periprocedural complication rates between the two navigation techniques.

2 Materials and Methods

2.1 Study population and design

We analyzed the anonymized data of a total of 939 consecutive procedures in 667 patients with AF between April 2006 and April 2016. In total 287 consecutive patients were ablated using remote magnetic navigated irrigated tip catheter (3.5 mm Navistar Thermocool® RMT, Biosense-Webster) for the ablation of AF between 2007 and 2014. We compared these patients with 380 subjects with manually navigated catheter ablation. Between 2006 and 2008 and in 136 patients, the ablation was performed with an irrigated-tip catheter (3.5 mm Navistar Thermocool®, Biosense-Webster) and between 2012 and 2016 by 244 subjects with an irrigated-tip surround flow catheter (3.5 mm Navistar Thermocool® SF, Biosense Webster). It is important to note, that the majority of our study population (60% of the patients) were enrolled with persistent AF at baseline, defined as AF lasting >7 days or requiring CV according to the guidelines at the time of the study (Camm et al. 2012).

2.2 Ablation procedure

All patients gave informed consent prior to the performed periinterventional diagnostics and for the ablation procedure. In every patient, LA thrombi were excluded by transesophageal echocardiography and contrast-enhanced high-resolution thoracic CT prior the ablation procedure. Furthermore, LA anatomy was acquired prior to the procedure for intraprocedural navigation. During the PVI we delivered a conscious sedation using intravenous sufentanil, midazolam and/or propofol under constant surveillance of oxygen saturation and blood pressure. During the procedure every catheter was introduced via the femoral veins. A 6F steerable decapolar catheter (Bard Dynamic Tip®, Bard Inc., Lowell, MA, USA) was placed in the coronary sinus. After a fluoroscopically assisted double TsP an SL1® sheath (St. Jude Medical, Inc., St. Paul, MN, USA) in the RMN group or an Agilis® deflectable sheath (St Jude Medical) in the MCN groups were positioned into the LA. In case of the RMN patients, a 3.5 mm open-irrigated, magnetic mapping and ablation catheter (Navistar Thermocool® RMT, Biosense-Webster, Diamond Bar, USA) was brought through the sheath into the LA, whereas in the MCN groups either a manually guided 3.5 mm open irrigated tip mapping and ablation catheter (Navistar Thermocool®, Biosense Webster) or a manually guided 3.5 mm open irrigated tip surround flow mapping and ablation catheter (Navistar Thermocool® SF, Biosense Webster) was utilized. In case of every ablation after January 2010 a circular mapping catheter was adapted as a common diagnostic device during every PV ablation. The circular mapping catheter (Lasso®, Biosense Webster, Diamond Bar, CA, USA) was placed within the PV ostium to monitor electrical activity during ablation and to verify electrical PV isolation. Intravenous heparin was used immediately after the TsP to reach and uphold an activated clotting time (ACT) of 300-350 s until the completion of the

procedure. Subjects hospitalized at the baseline with persistent AF were submitted to an electrical CV prior to 3D-mapping and PVI. Circumferential PVI was performed using a 3D mapping system (either CartoXP® or Carto3® RMT, Biosense Webster) in conjunction with the integrated CT image of the LA and real-time fluoroscopy. In the case of RMN subjects, the Niobe II® magnetic navigation system (Stereotaxis®) and a joystick-controlled motor drive (Cardiodrive®, Stereotaxis) was used for RMN of the ablation catheter, whereas by the MCN patients the ablation catheter was manipulated manually. In the case of persistent AF, supplementary ablation lines were considered during the repeat procedures at the discretion of the operator. RF current was utilized for 30–60s in a case of a lesion, applying 40 W (irrigation flow rate 30 ml/min) or 30 W at the posterior LA wall (irrigation flow rate 17 ml/min) with the generator (Stockert®, Biosense Webster) in a power-controlled mode and with an upper temperature limit of 45 °C in both groups. The acute clinical aim of the ablation procedure was the complete electrical isolation of all PVs defined as bidirectional conduction block. This was confirmed by the lasso catheter and a careful and repeated mapping for residual potentials around the entire circumference of the PV ostia and pacing from multiple sites within the circumferential line. All PVs were verified at the end of the procedure resulting in a waiting period of >30 min for the LSPV and LIPV and ca. 5 min for RSPV and RIPV. No drugs were used to illicit triggers or uncover dormant isolation. The same experienced operators accomplished all of the catheter ablations.

2.3 Follow-up

After the PVI and hospital discharge, an outpatient FU was organized and a 4-day continuous Holter electrocardiogram was repeated after 3, 6 and 12 months and on a 12-month basis thereafter. In total 112 (17.5%) of the subjects had an implanted cardiac device, which was interrogated by every inpatient control. At each inpatient control and in case of telephonic visit, patients were asked for subjective symptoms, externally documented arrhythmia episodes; also, the actual medication plan was assessed. Furthermore, all patients were instructed to present themselves immediately in case of cardiac symptoms suggestive for arrhythmia recurrence and obtain ECG documentation. A CV was implemented prior to discharge in case of AF/atrial tachycardia (AT) recurrence post-interventional for episodes lasting longer than 6 h. Furthermore, by individual subjects AADs (flecainide, propafenone, dronedarone, amiodarone) were continued for the first 3 post-interventional months (blanking period) with suspension of the AADs after the blanking period. A documented AF/AT episode lasting longer than 30 s after the blanking period was considered a recurrence. We defined the primary endpoint of our study as a recurrence of AF. In case of documented recurrence after the blanking period, FU was censored. In a case of crossover to the other treatment group by any repeat ablation, FU was also censored. Additionally, AF burden was also calculated from Holter ECGs and implantable event recorders (Reveal XT® and Reveal LINQ®, Medtronic, Fridley, MN). As a major complication we defined events

according to the international expert consensus (Cappato et al. 2005). In case of suspected periinterventional complications, additional diagnostic measures (e.g., echocardiogram, chest X-ray/CT) were implemented.

2.4 Statistical analysis

In our study, variables were expressed as mean ± standard deviation (SD) if normally distributed, or as percentage or median value with 25th and 75th percentiles interquartile range (IQR) in case of non-normal distribution. Differences in the frequency of characteristics were assessed by independent samples Student's t-test for continuous variables. Chi-square statistic (or Fisher's exact test if applicable) was used for discrete/categorical variables. Probability of AF recurrence was based on the time to first AF recurrence after the index procedure determined by Kaplan–Meier analysis with Mantel-Cox (Log-Rank) test. Time to first AF recurrence was plotted as a Kaplan–Meier curve. If a crossover between RMN and MCN groups occurred, FU was censored. A Cox proportional hazards model with multiple variables was performed to identify predictors of AF recurrence in a multivariable analysis at FU. Hazard was defined as hazard ratio (HR) and was depicted with as a confidence interval (CI). The studied parameters included catheter type, number of isolated PVs, age, LA diameter, type of AF, gender, prior CV, and prior AADs. All tests were performed with a two-tailed significance level of 0.05. We used SPSS 23.0 (SPSS®, Inc.) for data analysis.

3 Results

3.1 Baseline characteristics

380 patients in the MCN group underwent a mean 1.4 ± 0.7 procedures, in the case of RMN patients, 287 subjects had 1.4 ± 0.6 procedures (P=0.446). There were no significant differences comparing the baseline characteristics of the two treatment groups. The major baseline characteristics of the ablated groups are presented in Table 8.

	MCN (380)	***RMN (287)***	***P value***
Gender (male)	248 (65%)	174 (60%)	0.260
Age (years)	62.1±10.6	62.7±10.3	0.473
Paroxysmal AF	160 (41%)	105 (36%)	0.168
Persistent AF	221 (59%)	181 (64%)	0.168
BMI (kg/m^2)	28.9±5.0	28.5±5.5	0.340
Hypertension	299 (78%)	213 (74%)	0.226
CAD	82 (21%)	54 (18%)	0.402
COPD	29 (7%)	23 (8%)	0.837
OSAS	27 (7%)	17 (5%)	0.556
Hyperlipidemia	169 (44%)	120 (41%)	0.536
DM	48 (12%)	29 (10%)	0.325
LA size (mm)	45.8±7.1	46.6±6.5	0.125
LVEF (%)	56.6±8.1	56.3±6.9	0.619
Prior Cardioversion	264 (69%)	204 (71%)	0.295
Prior AADs	1.2±0.8	1.1±0.8	0.279
CAAP-AF Score	6.0±2.1	5.9±2.3	0.278

Table 8: Baseline characteristics of the patient groups (Schlögl et al. 2022b). Reproduced with the permission of John Wiley and Sons.

3.2 Procedural data

The ablation characteristics and FU data of both groups are summarized in Table 9. In case of RMN subjects, total procedure time, RF application time and total number of ablation points were significantly higher compared to the MCN patients. However, total fluoroscopy time and fluoroscopy dose were significantly lower by RMN guided cases compared to MCN subjects. The acute procedural success, defined as the complete electrical isolation of all PVs was achieved in only 75 % of the RMN-guided cases (303 out of 404 ablations) compared to 92% acute success in case of MCN guided procedures (491 out of 535 ablations; P<0.001).

	MCN (380)	***RMN (287)***	***P value***
Total procedure time (min)	201.5±76.7	224.8±50.7	**<0.001**
Fluoroscopy time (min)	50.5±29.4	15.7±11.5	**<0.001**
Fluoroscopy dose (Gycm²)	14071.5±8695.1	5615.9±3512.8	**0.021**
Radiofrequency time (min)	43.6±13	57.5±15.2	**<0.001**
Number of ablation points	49.8±18.3	61.0±19.5	**<0.001**
Major peri- and post-procedural complications	14 (2.7%)	9(3%)	0.842
Complete Isolation of all PVs (%)	91.7%	74.7%	**<0.001**
Total number of procedures	1.4±0.7	1.4±0.6	0.446
Follow up (months)	28.6±28.6	26.3±26.3	0.281
Mean Holter Recordings	3.7±3.1	4.3±3.6	0.061

Table 9: Characteristics of ablation and follow-up in the patient groups (Schlögl et al 2022b). Reproduced with the permission of John Wiley and Sons.

3.3 Complications

A cumulative number of 23 patients developed a major peri-or post-procedural complication: in total 9 (3.0%) in the RMN guided cases and 14 (2.7%) in the MCN group (P=0.842; Table 10). Detailed, after RMN ablation one patient experienced pericardial effusion requiring pericardiocentesis after the ablation. Two patients developed a pericardial effusion during the TsP, one later dying of complications. Post-procedural stroke was registered in two cases, thereof one with associated with heparin induced thrombocytopenia. One patient suffered from a postprocedural subsegmental pulmonary embolism. By three cases, blood transfusion was required after a peri-procedural bleeding, however no surgical intervention

was indicated. In the case of MCN patients, seven cases developed a pericardial effusion after the ablation requiring pericardiocentesis. One patient developed a femoral arteriovenous fistula and one patient an aneurysm of the femoral artery, both of these complications requiring surgical therapy later. One subject developed a groin bleeding complicated with an infection of the hematoma, also requiring surgical intervention. Blood transfusion was necessary in four patients after a peri-procedural bleeding. Atrio-esophageal fistula did not occur in any of our cases.

Safety endpoint	*RMN (287)*	*MCN (380)*	*P value*
Pericardial effusion	3 (1%)	7 (1.8%)	n.s.
Post-procedural stroke	2 (0.6%)	0 (0%)	n.s.
Pulmonary embolism	1 (0.3%)	0 (0%)	n.s.
Femoral arteriovenous fistula aneurysm requiring surgical intervention	0 (0%)	1 (0.2%)	n.s.
Postprocedural aneurysm/bleeding requiring surgical intervention	0 (0%)	2 (0.5%)	n.s.
Atrio-esophageal fistula	0 (0%)	0 (0%)	n.s.

Table 10: Safety Endpoints

3.4 Follow up

The most important data about follow up are summarized in Table 7. In total 31 patients (4.6%) were lost to FU. There was no significant difference in the mean number of Holter recordings per patient (P=0.061) or in the mean follow up time (P=0.281) between our groups. In a total of 105 cases (10%) the follow up was censored as a result of a crossover between the groups; almost exclusively by a crossover from the RMN group to the MCN guided group by a redo procedure.

3.5 Recurrence rates

The primary endpoint was reached in the first year after the blanking period by 471 cases (49%). In 107 (11%) cases, the recurrence of the AF was documented in the second year. In 128 patients (14%), a recurrence of AF was registered after the second year of FU. Only 107 cases (11.4%) did not reach the primary endpoint after the ablation during the FU period. Time to recurrence after the ablation procedure differed significantly between the RMN cases and MCN patients regardless to first or repeat procedures (P<0.001, Figure 8).

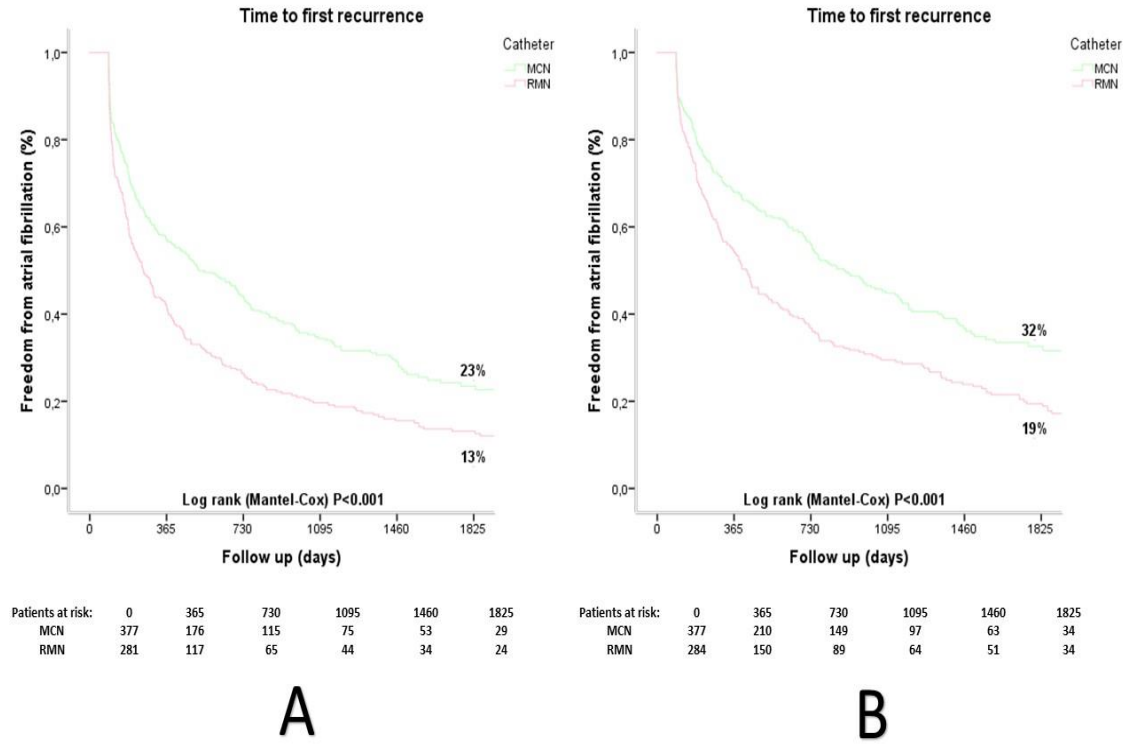

Figure 8: Freedom from atrial fibrillation after (A) first and (B) any procedure (Schlögl et al 2022b). Reproduced with the permission of John Wiley and Sons.

Analyzing only those ablation procedures where an acute procedural success (the complete isolation of every PVs) was reached, time to first documented AF/AT recurrence after RMN guided ablations was still significantly shorter (P<0.001, Figure 9).

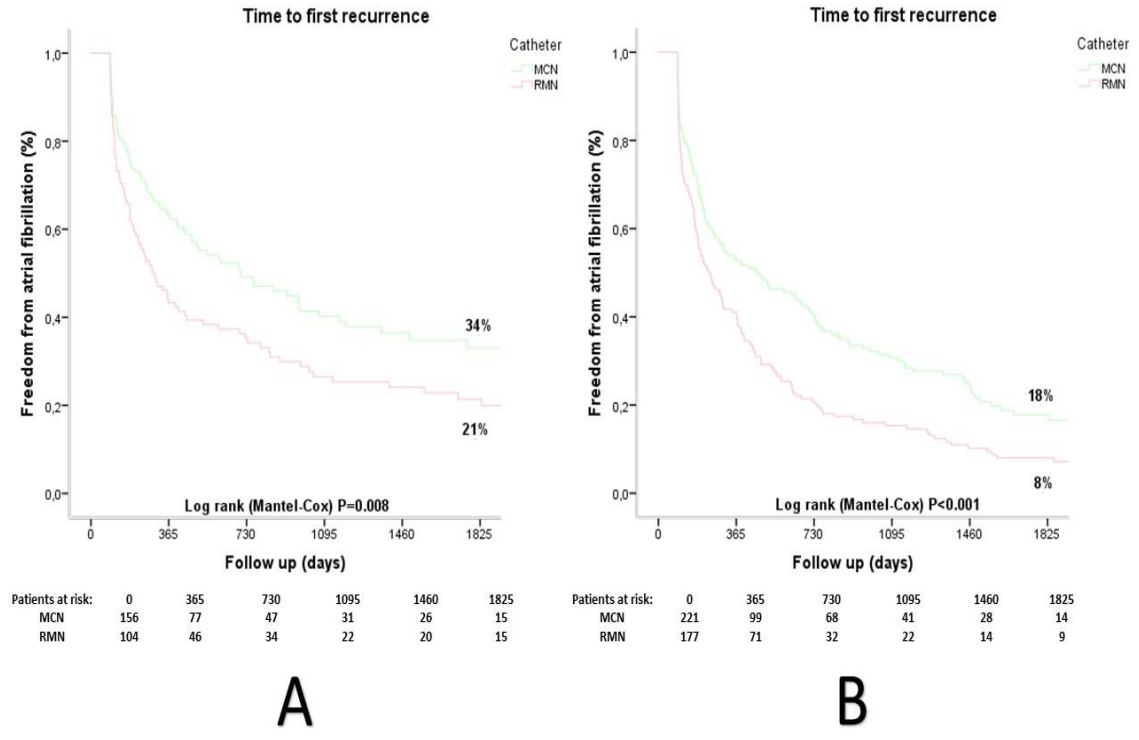

Figure 9: Freedom from atrial fibrillation after (A) first procedure in patients with

acute success (B) any procedure in patients with acute success (Schlögl et al 2022b). Reproduced with the permission of John Wiley and Sons.

Grouping the cases as paroxysmal and persistent AF cases, a statistically significant shorter time to first recurrence by the RMN guided patients was still identifiable (P=0.008 for paroxysmal AF; P<0.001 for persistent AF, Figure 10).

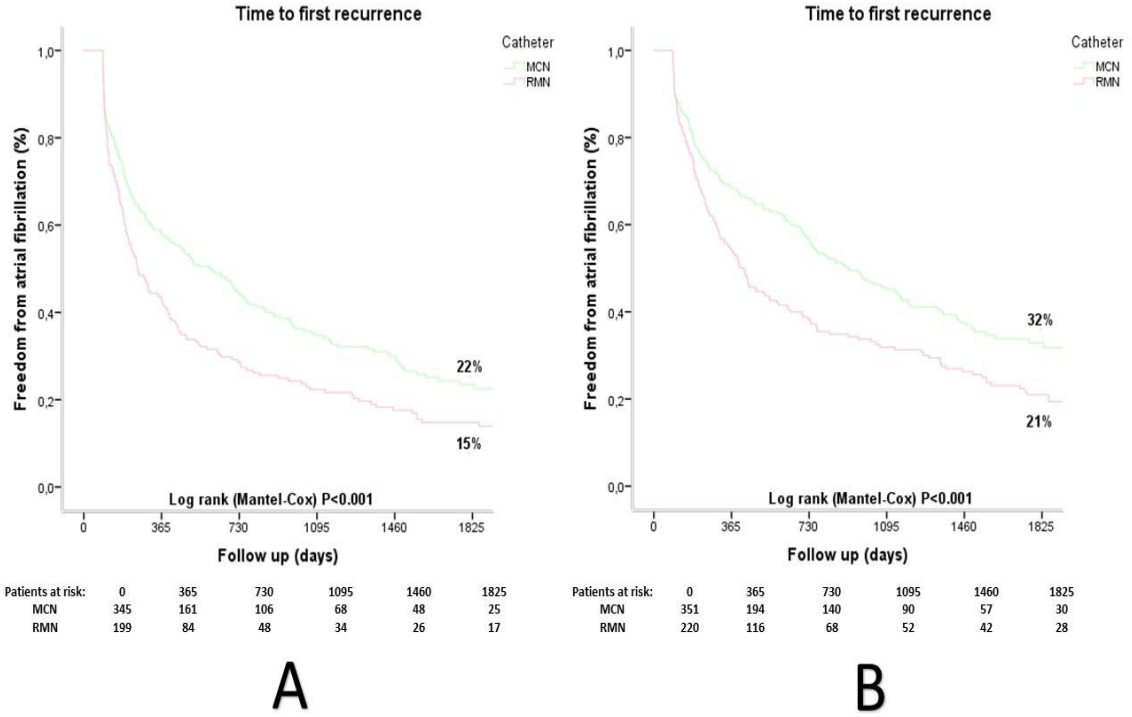

Figure 10: Freedom from atrial fibrillation after (A) first procedure in patients with paroxysmal atrial fibrillation (B) first procedure in patients with persistent atrial fibrillation (Schlögl et al 2022b). Reproduced with the permission of John Wiley and Sons.

To define the independent predictors of AF recurrence, a multivariate Cox regression analysis was implemented. In this model, we incorporated the significant univariant predictors of AF recurrence (number of isolated PVs, age, persistent AF, RMN guided procedure, left atrial size, gender and prior cardioversion). In the multivariate model, incomplete isolation of the PVs, remote magnetic catheter navigation, age, persistent AF and LA diameter were independently associated with a higher risk of recurrence of AF (Table 11).

	HR	***CI***	***P-Value***
Number of isolated PVs	0.841	0.765-0.925	**0.001**
Age	1.019	1.011-1.027	**0.001**

Persistent AF	1.367	1.095-1.707	**0.006**
RMN	1.239	1.054-1.457	**0.010**
Left atrial size	1.013	1.001-1.026	**0.029**
Gender	1.171	0.994-1.379	0.059
Prior cardioversion	0.987	0.780-1.249	0.914
Failed AADs	0.952	0.793-1.243	0.952

Table 11: Independent predictors of AF recurrence (Schlögl et al 2022b). Reproduced with the permission of John Wiley and Sons.

Lastly, we summarized the available Holter ECGs and the device interrogations of implanted devices before and after the ablation to analyze the AF burden by our patients. There was no significant difference in AF burden between the RMN cases and MCN guided cases before the procedure. After the procedure, there was a significant reduction in the AF burden by both groups, however the RMN patients had a significantly higher AF burden compared to the MCN group (Table 12).

AF Burden	***Mean before PVI***	***Mean after PVI***	***P-Value***
RMN cases	36%	26%	0.913
MCN cases	36%	16%	0.001

Table 12: AF burden compared between the two groups

3.6 Repeat ablations

We analyzed the redo ablations during the FU. There was a significantly higher rate of reconnections after RMN cases (P<0.001, Figure 11,12) compared to MCN subjects. Furthermore, we analyzed the number of PVI reconnections. There was as significant higher trend in the median number of reconnected veins between groups in the RMN group (P<0.001, Table 13).

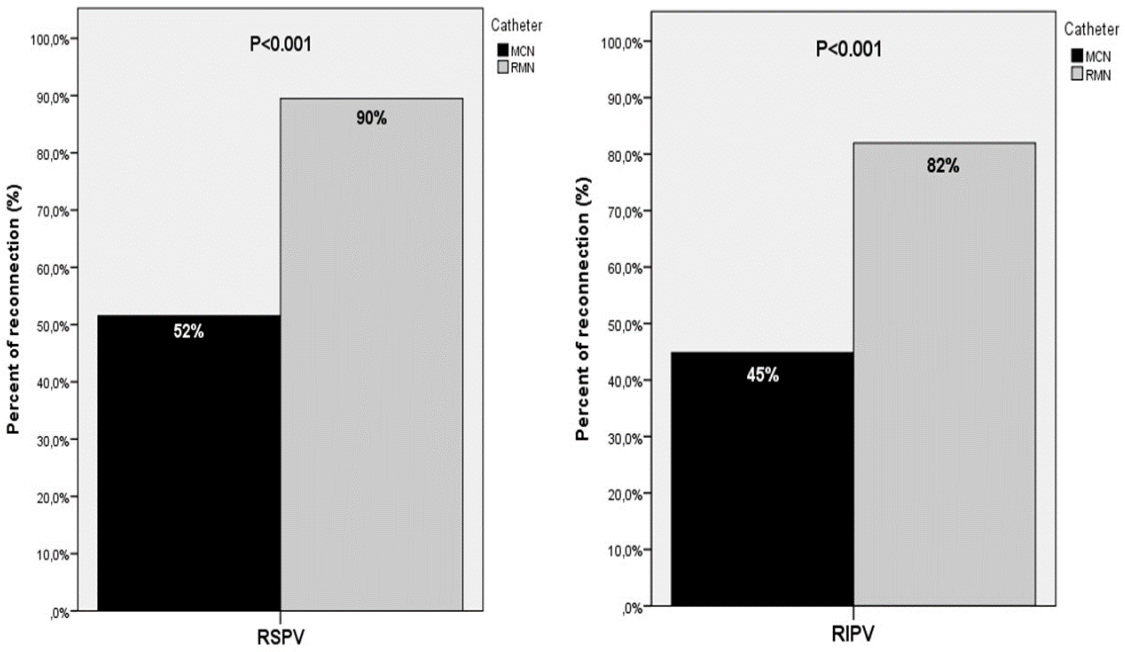

Figure 11: Reconnection rate of the right pulmonary veins in redo procedures (Schlögl et al 2022b). Reproduced with the permission of John Wiley and Sons.

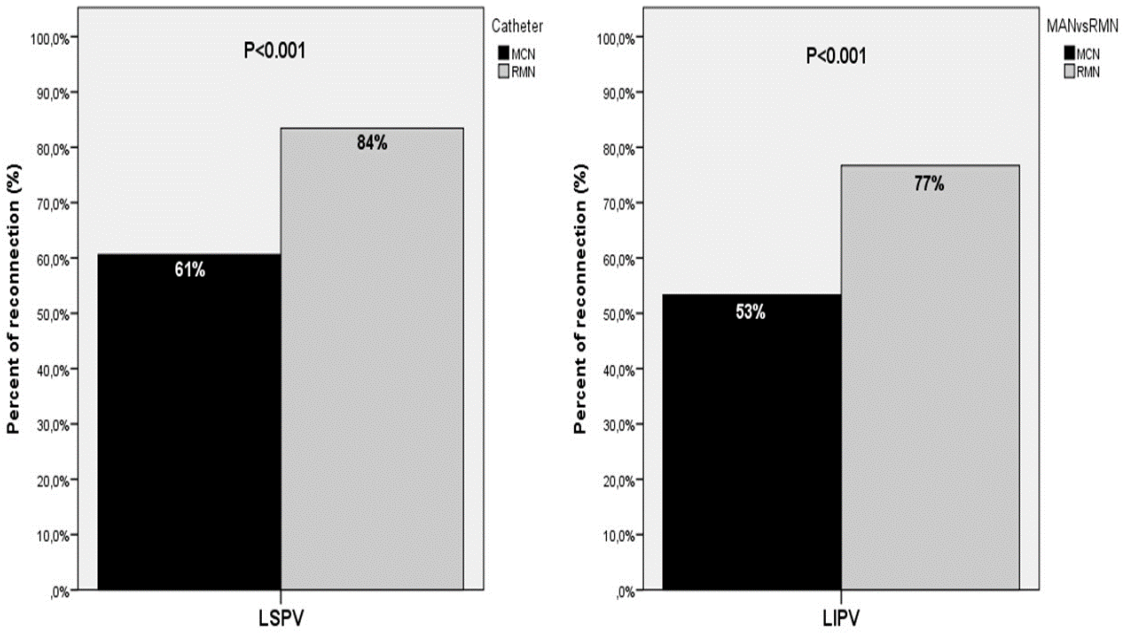

Figure 12: Reconnection rate of the left pulmonary veins in redo procedures (Schlögl et al 2022b). Reproduced with the permission of John Wiley and Sons.

Reconnected veins	***RMN***	***MCN***	***P-Value***
Median	median 4	median 3	P<0.001
IQR	IQR 3–4	IQR: 2–3	
Range	0-4	0-4	

Table 13: Characteristics of reconnected veins by redo procedures

3.7 Learning curve

Lastly, we analyzed the available ablations to detect any learning curve effect in the groups. This data has been summarized in Table 14. It is important to note, that the procedure was performed by the same experienced electrophysiologists. We compared the first 50% of the ablations (first half) to the last 50% ablation (second half) within the navigation method to detect any hidden learning curve effect. We registered a significant learning curve effect by the MCN approach leading to faster ablations in the second half of the ablation group. However, there was a hint of a possible learning curve effect in case of magnetic navigation as well because significantly more ablation points were available in the same total procedure time and total ablation time.

Learning curve	***RMN first half***	***RMN second half***	***P-Value***	***MCN first half***	***MCN second half***	***P-Value***
Total procedure time (min)	226±55	224±59	0.895	186±73	126±37	**<0.001**
Total fluoroscopy time (min)	16±10	17±13	0.642	57±72	19±6	**<0.001**
Total ablation time (min)	59±17	51±19	0.133	37±15	22±11	**<0.001**
Total ablation points (points)	58±20	64±26	**0.022**	44±19	35±18	**<0.001**

Table 14: Analysis of the learning curve effect

4 Discussion

4.1 Primary findings

The main finding of our study is a significant higher AF recurrence rate of RMN-guided PVI compared to the MCN guided approach. To the best of our knowledge, this is the first study of a large cohort of patients with a long-term FU comparing RMN to MCN showing a significant difference regarding long term success after adjusting for multiple confounders of PVI success rates. Moreover, our study is the first analyzing the rate of PV reconnections in a large patient cohort after RMN assisted PVI. Importantly, compared to previous studies, most of our patients (60%) presented with persistent AF.

4.2 Literature overview

The feasibility, safety and efficacy of RMN-guided RFCA in AF has been well demonstrated in the first index study (Pappone et al. 2006). Previous comparisons of RMN guided PVI to MCN guided approach were often conducted on rather small patient collectives with short FU time with the majority of patients presenting with paroxysmal AF (Katsiyiannis et al. 2008; Miyazaki et al. 2010; Sorgente et al. 2010; Arya et al. 2011; Choi et al. 2011; Lüthje et al. 2011; Solheim et al. 2011; Koutalas et al. 2015; Adragão et al. 2016; Weiss et al. 2016; Kataria et al. 2017; Yuan et al. 2017; Jez et al. 2020) (Table 15). Meta-analyses included all available studies (Proietti et al. 2013; Jia et al. 2019; Virk et al. 2019) to date. Based on the available research data, Proietti et al. (2013) questioned if previous studies would be conclusive on the effectiveness of RMN guided PVI compared to MCN guided approach. Despite this approach is being used over a decade in clinical praxis, magnetic navigation for PVI has never been compared to conventional manual ablation in a large randomized multicenter controlled trial.

Study	*Method*	*Population*	*Persisting AF (%)*	*Follow up (months)*	*Freedom from AF*
Katsiyiannis et al. 2008	Prospective observational	40 (20 RMN, 20 MCN)	unknown	12	80% RMN, 75% MCN (P=n.s.)
Miyazaki et al. 2010	Retrospective	74 (30 RMN, 44 MCN)	unknown	12	69% RMN, 61% MCN (P =0.961)
Sorgente et al. 2010	Retrospective	64 (35 RMN, 29 MCN)	16% RMN, 24% MCN	12±6	66% RMN, 65% MCN (P=n.s.)
Arya et al. 2011	Retrospective	356 (70 RMN, 286 MCN)	50% RMN, 25% MCN	6	57% RMN, 66% MCN (P =0.196)

Choi et al. 2011	Retrospective	101 (41 RMN, 71 MCN)	41% RMN, 38% MCN	3	83% RMN, 83% MCN (P =0.82)
Lüthje et al. 2011	Prospective observational	161 (107 RMN, 54 MCN)	68% RMN 67% MCN	12	53% RMN, 55% MCN (P =0.57)
Solheim et al. 2011	Retrospective	88 (49 RMN, 65 MCN)	35% RMN, 31% MCN	12±5	53% RMN-NIC, 61% RMN-IC, 60% MCN, 53.8% (P=n.s.)
Koutalas et al. 2015	Retrospective	140 (70 RMN, 70 MCN)	65% RMN, 65% MCN	29±19	
Adragão et al. 2016	Retrospective, propensity score matching	574 (287 RMN, 287 MCN)	26% RMN, 28% MCN	31±18	59% RMN, 55% MCN (P=n.s.)
Weiss et al. 2016	Retrospective	627 (315 RMN, 312 MCN)	42% RMN, 46 %MCN	12	38% RMN, 40% MCN (P=0.68)
Kataria et al. 2017	Retrospective	336 (114 RMN, 222 MCN)	0%	27±8	70% RMN, 69% MCN (P= 0.61)
Yuan et al. 2017	Retrospective	214 (112 RMN, 102 MCN)	30% RMN, 29% MCN	39±9	1y, 2y, 3,5y: 63%, 46%, 42% RMN vs. 60%, 32%, 30% MCN (P<0.05)
Jez J et al. 2020	Retrospective	146 (57 RMN, 89 MCN)	unknown	6	Paroxysmal AF 60% RMN, 73% MCN (P=0.42) Persistent AF 69% RMN, 75% MCN (P=0.77)

Table 15: Summary of the available studies

In detail, Arya et al. (2011) presented retrospective data enrolling a large number of patients showing no significant difference in AF efficacy between the two approaches 66% vs 58%, respectively). However, FU was limited only for six months and the number of RMN cases low. A prospective study of our own center enrolling a small number of subjects over 12 months showed no difference in case of efficacy between the approaches (Lüthje et al. 2011). This patient cohort was the foundation of our present study cohort which expanded and now includes all RMN and MCN ablations between 2006 and 2016. Weiss et al. (2016) enrolled 627 patients reporting no difference between the two groups regarding freedom from AF after 1 year of FU. However, this study included almost only patients with paroxysmal AF. Kataria et al. (2017) reported on a cohort of 336 patients exclusively with paroxysmal AF with a long-term FU showing no difference between RMN guided approach

and MCN guidance regarding the AF recurrence. Yuan et al. (2017) compared 214 patients over a long-term FU, showing significantly higher rates of freedom from AF after an RMN guided PVI. Although this study demonstrated the longest mean FU, the patient cohort was smaller than the present study and consisted mostly of paroxysmal AF cases. Adragão et al. (2016) published a significant number of cases after propensity score matching with a long FU showing no significant difference in the AF recurrence rate between the approaches. However, the presented cases were also mostly of paroxysmal AF. Koutalas et al. (2015) reported from 140 patients matched for patient characteristics at baseline, with a long mean FU. Similar to our study, there was a significant difference in the time to the first AF recurrence between the approaches. Furthermore, in the multivariable Cox-Regression model the only factor independently and significantly influencing an AF recurrence was RMN guidance (HR 1.59, 95% CI 1.004–2.52, P=0.048). Most importantly, this was the only patient cohort so far showing higher freedom from AF at the follow up after MCN PVI compared to the RMN guided approach.

4.3 Possible factors of RMN efficacy

In the context of possible explanations for the lower acute and long-term success of RMN-PVI in our study several factors should be mentioned. First and foremost, circumferential continuous ablation lines aim to electrically disconnect the PV antrum from the body of the LA. In cases, where these goals are not achieved, PVs are either partly or remain only temporarily isolated, leading to an increased chance of AF recurrence (Calkins et al. 2018). As it was proven by previous studies (Piorkowski et al. 2011; Koutalas et al. 2015), flexibility of the magnetic catheter shaft may result in a reduction of the maximal force applied to the tissue. As a result of anatomical complexities and the relationship of the ostium of the RIPV to the insertion of the transseptal sheath by the entry point in the LA, circular mapping catheter-guided PVI can be demanding during the RMN procedures (Miyazaki et al. 2010). Isolation of the right PVs can be thus resulting in longer procedure time and occasional unfeasible isolation of the right PVs (Miyazaki et al. 2010). Regarding acute procedural success (namely the complete electrical isolation of all PVs) after RMN there is a large discrepancy between the previous studies showing results between 43% and 100% (Jia et al 2019). We summarized the most important studies according to acute success in Table 16. However, numerous studies did not report on acute procedural success.

Studies	***Acute success after PVI***
Pappone et al. 2006	95%
Di Biase et al. 2007	92%
Sorgente et al. 2010	100%
Miyazaki et al. 2010	87%
Choi et al. 2011	85%

Arya et al. 2011	87%
Lüthje et al. 2011	92%
Kataria et al. 2017	100%
Adragão et al. 2016	100%

Table 16: Acute success in previous studies

In our study there was a significantly lower complete isolation rate of PVs after RMN procedures compared to MCN. Upon multivariate analysis (Table 11) adjusted for the number of isolated veins, RMN remains a significant independent factor for AF recurrence. Therefore, the higher rate of AF/AT recurrence after RMN cannot only be ascribed to the lower acute success rate. Secondly, RF application time and the number of application points were increased in the RMN group, probably indicating lower tissue CF. Aagaard et al (2015) has already published a study about the insights of lesion creation before. Reflecting to these results, Bessière et al. (2018) accounted that the CF averages by RMN are laying approximately by 6 g, with similar results obtained using transvenous and retrograde approaches with 0.08 T and 0.10 T magnetic field, thus obtaining lower values than during a standard manually navigated ablation procedures (e.g. 10–12 g) (Bun et al. 2017). Translating CF into the clinical efficacy à la Reddy et al. (2012), freedom from AF after PVI at 12-months FU was superior in patients with higher average CF. It can be assumed, that RMN has a flawed effectiveness to create ideal ablation lesions due to reduced average force applied thus leading to decreased clinical efficacy. Thirdly, after analyzing the repeat procedures we could identify, that there was a significantly higher rate of PV reconnections after RMN ablation (Figure 11,12). In accordance with our first point of debate, the right PVs were more prone to reconnection after RMN. This could be also a hint of reduced average force of the magnetic navigated catheters due to a more challenging anatomy.

4.4 Safety aspects of RMN ablation

Matching the meta-data published by Virk et al. (2019); magnetic navigation led to considerably shorter fluoroscopy duration, however to longer ablation times. However, novel MCN catheters and CF sensing technology combined with fluoroscopy-lowering strategies leads also to significantly lower fluoroscopy time (Schlögl et al. 2022a), matching the data of RMN approach. This leaves us to hypothesize, that the effect of magnetic navigation on fluoroscopy duration may be annulled compared to the newest generation of catheters. It is also evident from our data, that an increased RF current must be delivered by the magnetic guided approach to achieve the same clinical effect, reflecting to the argument of lower average CF during RMN ablation. The ratio of complications in our center are like those previously published by Cappato et al. (2005; 2010) and in line with the metanalyses of published RMN data (Jia et al. 2019; Virk et al. 2019). As previously published by Virk et al (2019), periprocedural safety is an undeniable edge of RMN. Magnetic navigation led to a

significant reduction of major periprocedural risk (Virk et al. 2019). In our study, complication risk was statistically not different across the groups. However, it is important to note, that we registered a lower number of pericardial effusions after RMN guided ablation, similar to the previously published data (Virk et al. 2019) (Table 10). We could hypothesize, that the reduction of shear atrial wall stress and lower contact force plays a major role in this beneficiary effect of RMN assisted ablation.

4.5 Learning curve

Lüthje et al. (2011) reported of a significant reduction of fluoroscopy time over the course of the RMN experience. Kataria and his colleagues (2017) did not find a learning curve effect over time. According to our data, there was a significant reduction of every procedure characteristic in case of MCN group in the second half of the ablations. However, by RMN ablations, only the number of ablation points were significantly higher over time during the experience. A possible explanation for the MCN data is the required dexterity which is developed over time furthering the ablation efficacy by the operator. Interestingly, more points available in the same mean procedure time by RMN hints also about experience developed over time, although this was not in connection with the other procedural characteristics. More ablation points available over time with experience in the RMN group also aligns well with our previous indirect findings about lower force available/ablated point leading to decreased efficacy, leaving the operator in need of more points to be able to achieve the primary endpoint of acute success.

4.6 Limitations

Our data represents a non-randomized single-center observational experience, thus leaving room for unknown biases. The exact number of documented and detected AF recurrences were in a way reliant on the alertness of the study subject and family doctor. As a result, silent AF recurrences may have stayed hidden. Available Holter ECGs and cardiac implanted devices was used to determine AF burden, however continuous monitoring was only available by one fifth of the study population. The use of CF measurements and ablation index during PVI were not yet available at the time of the study, therefore these advances are not yet represented in our experiences.

5 Conclusions

The direct comparison of RMN to MCN has been mainly discussed based on small case series and retrospective studies analyzing patients with paroxysmal atrial fibrillation. A randomized multicenter controlled trial is still lacking to this day.

Our large observational cohort was the first to compare RMN to MCN mainly by persistent AF during a long-term FU. In our data, PV ablation using RMN has a higher rate of PV reconnections, higher AF recurrence rates and increased procedural time compared to MCN. Complication rates did not significantly differ between RMN compared to MCN, while total fluoroscopy time was significantly lower using RMN. There was a significant detectable learning curve effect in case of manual approach compared to RMN.

Our data is helpful to reignite the discussion about the role of RMN in the ablation of atrial fibrillation, especially as new MCN catheters are becoming increasingly available which provide even more improved efficiency and safety.

Before routine use and widespread adoption of new technologies, carefully planned multicenter randomized controlled studies are needed to precisely estimate the clinical impact and to facilitate a discussion.

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Danksagung

Mein Dank gilt einer großen Zahl von Menschen, ohne die diese Arbeit nicht zustande gekommen wäre. Herrn Prof. Dr. Gerd Hasenfuß danke ich sehr herzlich für die Möglichkeit, diese Arbeit in seiner Klinik zu verfassen. Ganz besonders danke ich Prof. Dr. Markus Zabel für die Überlassung des Themas dieser Arbeit und die ausgezeichneten Möglichkeiten, es zu bearbeiten, ohne seine Rückendeckung und unsere vielen, immer wieder auch kritischen Diskussionen wäre diese Arbeit nicht möglich gewesen.

Weiterhin möchte ich mich dem gesamten Team der Klinischen Elektrophysiologie und der EU-CERT-Studie für die freundschaftliche und motivierende Unterstützung danken.

Letztendlich bedanke ich mich an meiner Frau, Klaudia Stella Schlögl für ihre unendliche Unterstützung.