

PRIIT PAUKLIN

Hemodynamic and biochemical  
characteristics of patients with atrial  
fibrillation and anticoagulation  
of  $\geq 65$ -year-old patients  
with atrial fibrillation in Estonia



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Press

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## LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications referred to in the text by their Roman numerals (I–III):

- I Pauklin P, Eha J, Tootsi K, Kolk R, Paju R, Kals M, Kampus P. Atrial fibrillation is associated with increased central blood pressure and arterial stiffness. *Journal of Clinical Hypertension (Greenwich)*. 2021; 23(8):1581–1587.
- II Pauklin P, Zilmer M, Eha J, Tootsi K, Kals M, Kampus P. Markers of Inflammation, Oxidative Stress, and Fibrosis in Patients with Atrial Fibrillation. *Oxidative Medicine and Cellular Longevity*. 2022; 2022:4556671.
- III Pauklin P, Marandi T, Kals M, Ainla T, Martinson K, Eha J, Kampus P. Lifeday coverage of oral anticoagulants and one-year relative survival in patients with atrial fibrillation: a population-based study in Estonia. *BMC Cardiovascular Disorders*. 2023;23(1):398.

### **Author's contribution:**

Papers I–III: Involvement in the study design, collecting clinical data, data analysis, and writing the paper.

## ABBREVIATIONS

ACEI	angiotensin converting enzyme inhibitor
AF	atrial fibrillation
AIx	augmentation index
AIx@75	augmentation index corrected for a heart rate of 75 beats/minute
AP	augmentation pressure
ARB	angiotensin II receptor blocker
AS	arterial stiffness
BB	beta-blocker
BD	<i>bis in die</i> ; twice a day
BNP	B-type natriuretic peptide
BP	blood pressure
CAD	coronary artery disease
cBP	central blood pressure
CCB	calcium channel blocker
cfPWV	carotid-femoral PWV
CO	cardiac output
cPP	central pulse pressure
CRP	C-reactive protein
cSBP	central systolic blood pressure
CV	cardiovascular
CVD	cardiovascular diseases
ECG	electrocardiogram
ECM	extracellular matrix
EF	left ventricular ejection fraction
eGFR	estimated glomerular filtration rate
EHIF	Estonian Health Insurance Fund
ELISA	enzyme-linked immunosorbent assay
ESC	European Society of Cardiology
Gal-3	galectin-3
GTF	generalized transfer function
HDL	high-density lipoprotein
HF	heart failure
HOCl	hypochlorous acid
HR	heart rate
hsCRP	high-sensitive C-reactive protein
HT	arterial hypertension
ICD-10	International Statistical Classification of Diseases 10th revision
IL-8	interleukin 8
INR	international normalized ratio
LA	left atrial
LAA	left atrial appendage
LDC	lifeday coverage

LDL	low-density lipoprotein
LOX-1	lectin-like oxidized low-density lipoprotein receptor-1
MAP	mean arterial pressure
MDA-LDL	malondialdehyde-modified low-density lipoprotein
MMP	matrix metalloproteinase
Mox-LDL	myeloperoxidase-oxidized lipoproteins
MPO	myeloperoxidase
NO	nitric oxide
NOAC	novel oral anticoagulant
NT-proBNP	N-terminal pro-brain natriuretic peptide
OAC	oral anticoagulant
OD	<i>omne in die</i> ; once a day
OSA	obstructive sleep apnea
oxLDL	oxidized low-density lipoprotein
OxS	oxidative stress
PAD	peripheral artery disease
PAI-1	plasminogen activator inhibitor 1
pBP	peripheral blood pressure
PP	pulse pressure
PPA	pulse pressure amplification
pPP	peripheral pulse pressure
pSBP	peripheral systolic blood pressure
PVI	pulmonary vein isolation
PWA	pulse wave analysis
PWV	pulse wave velocity
SD	standard deviation
SE	standard error
SR	sinus rhythm
TIA	transient ischemic attack
TNF $\alpha$	tumor necrosis factor $\alpha$
TTR	time in therapeutic range
VKA	vitamin K antagonists

# 1. INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the world (Hindricks *et al.* 2021). At the same time, it causes a major socio-economic burden to the population as it is associated with considerable morbidity and mortality (Hindricks *et al.* 2021).

Currently, the prevalence of AF ranges from 2–4% in the adult population worldwide (Benjamin *et al.* 2019), and it is estimated that we could expect a 2.3-fold increase in the coming decades (Chugh *et al.* 2014). One in three individuals at the age of 55 is predicted to develop AF during their lifetime (Staerk *et al.* 2018).

The pathophysiological mechanisms that lead to the development of AF are complex and not yet fully understood. The risk of AF is dependent on age, health behavior, and concomitant diseases, but also genetic factors that interlink with each other (Allan *et al.* 2017). Some of these factors are non-modifiable but many are, leading to the need to intervene early in the development of AF to decrease its incidence. Besides many important non-modifiable risk factors like age and sex, arterial hypertension (HT) seems to be a major modifiable contributor to AF (Kirchhof *et al.* 2012; Allan *et al.* 2017).

HT is the most common modifiable cardiovascular (CV) risk factor related to increased CV morbidity and mortality and a leading cause of premature death globally (Williams *et al.* 2018). The overall prevalence of HT is high, at around 30–45% in adults (Chow *et al.* 2013). It is well established that HT has an independent association with the incidence of many other CV events and diseases like coronary artery disease (CAD), stroke, sudden death, heart failure (HF), or peripheral artery disease (PAD) (Lewington *et al.* 2002). Newer evidence has also shown an increased risk of developing AF in patients with HT (Lip *et al.* 2017).

Peripheral blood pressure (pBP) measurement from the brachial artery is the standard for assessing blood pressure (BP) values. However, there can be significant differences between the BP in the peripheral and the central arteries. This is due to the BP amplification phenomenon that is closely related to arterial stiffness (AS) (Avolio *et al.* 2009). AS and central blood pressure (cBP) are increasingly recognized as important risk factors for cardiovascular disease (CVD) (Laurent *et al.* 2003; Vlachopoulos *et al.* 2010; Townsend *et al.* 2015) and seem to better correlate with CVD risk than pBP (Roman *et al.* 2007), yet have rarely been studied in patients with AF. It has also been shown that different antihypertensive medications may impact cBP and pBP differently. While angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and calcium channel blockers (CCBs) have been shown to reduce cBP and pBP to the same extent (Protogerou *et al.* 2009), data about beta-blockers (BBs) is more controversial (Kampus *et al.* 2011) because of the heterogeneity of this class of drugs. As BBs are the first choice of drugs for rate and rhythm control in AF, then this might also play an important role in the prognosis and residual CV risk of these patients (Xie *et al.* 2017).

On the cellular and tissue level, AF is related to electrical and structural remodeling processes that help to induce and maintain this arrhythmia (Korantzopoulos *et al.* 2018). Accumulating evidence has proposed an important role of inflammation (Guo *et al.* 2012; Hu *et al.* 2015) and oxidative stress (OxS) (Korantzopoulos *et al.* 2007; Samman Tahhan *et al.* 2017; Korantzopoulos *et al.* 2018; D’Oria *et al.* 2020) processes in the pathophysiological mechanisms that may lead to atrial fibrosis and AF. Biomarkers related to inflammation, OxS, and fibrosis have emerged as a newer research field to better understand the changes in the atria and the interactions of these mechanisms inducing tissue fibrosis. Ablation strategies for the rhythm management of AF patients are expensive and the effectiveness depends on the degree of atrial remodeling. That is why the potential prognostic role of biomarkers to assess success of therapy or interventions is of great clinical importance and would help to better select patients who would benefit the most from different treatment strategies.

AF is related to a five-fold increase in stroke risk in general, but the risk is heterogeneous among the patients and related to other comorbidities and risk factors that modify this risk (Pisters *et al.* 2012; Hindricks *et al.* 2021). Many risk scores have been developed to assess the individual risk of stroke, the most used being the CHA<sub>2</sub>DS<sub>2</sub>-VASc score (Hindricks *et al.* 2021). According to guidelines, patients with high risk (CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$ ; (Eesti Haigekassa Ravi-juhendite nõukoda 2018)) need life-long anticoagulation using preferably novel oral anticoagulants (NOACs) for stroke prevention (Hindricks *et al.* 2021; Steffel *et al.* 2021). Despite the clear benefit of these drugs, their wide availability, and ease of use, registries of AF like GARFIELD-AF show that oral anticoagulants (OACs) are still underused (Apenteng *et al.* 2013; Bassand *et al.* 2021). These large registries rely on self-reported use of OACs and their real-life use is not known (Steinberg *et al.* 2017). No registries exist that describe the nationwide use of anticoagulants in Estonia for stroke prevention in AF patients.

The main purpose of the present dissertation was to describe the biochemical and hemodynamic changes in patients with AF, as well as to assess the current state of anticoagulation of  $\geq 65$ -year-old AF patients in Estonia.

## 2. REVIEW OF THE LITERATURE

### 2.1. Atrial fibrillation

AF is to date the most common arrhythmia in clinical practice (Hindricks *et al.* 2021). Due to the increasing age of the worldwide population and better tools to detect the disease, the prevalence of AF is increasing and is seen in 2–4% of adults (Benjamin *et al.* 2019). As AF shares many risk factors (HT, diabetes, HF, CAD, obesity, and obstructive sleep apnea (OSA) (Lip *et al.* 2017; Heijman *et al.* 2021; Hindricks *et al.* 2021)) with other CVDs, a 2.3-fold rise of the disease is expected in the coming decades (Chugh *et al.* 2014).

The diagnosis of AF requires the documentation of the rhythm disturbance with an electrocardiogram (ECG) tracing lasting at least 30 seconds or an entire conventional 12-lead ECG (Hindricks *et al.* 2021).

The clinical presentation of patients with AF varies to a great extent. About 50–87% of patients can be initially asymptomatic (Boriani *et al.* 2015; Freeman *et al.* 2015; Siontis *et al.* 2016). Many have various symptoms like palpitations, dyspnea, fatigue (McCabe *et al.* 2011; Gleason *et al.* 2018), and some patients can present with hemodynamic instability (Long *et al.* 2018).

AF is not a benign disease. Over 60% of AF patients have an impaired quality of life or decreased exercise tolerance (Freeman *et al.* 2015; Blum *et al.* 2017; Walters *et al.* 2019), and 17% display disabling symptoms (Freeman *et al.* 2015). AF patients have a 10–40% annual hospitalization rate (Meyre *et al.* 2019), which is twice as much as age- and sex-matched individuals without AF (Kim *et al.* 2011). The stroke risk related to AF is highly dependent on comorbid conditions and is estimated to be about 20–30% of all ischemic strokes, but cardioembolic stroke is usually severe with a high rate of recurrence and leads frequently to permanent disability or death (Lin *et al.* 1996; Chao *et al.* 2016; Pistoia *et al.* 2016; Ceernodolea *et al.* 2017).

HF is frequently seen in patients with AF due to a combination of common risk factors and arrhythmia related alterations of the left ventricle. About 20–30% of patients have HF, and the combination of these two diseases leads to a significantly higher mortality than either of these conditions alone (Ziff *et al.* 2018). At the same time, AF is independently linked to an increase of all-cause mortality of about twofold in women and 1.5-fold in men (Stewart *et al.* 2002; Andersson *et al.* 2013), and an overall 3.5-fold increase in mortality has been seen in AF patients in a community-based European study (Magnussen *et al.* 2017).

The AF guidelines propose a streamlined “ABC pathway” (“A” Anticoagulation / Avoid stroke; “B” Better symptom management; “C” Cardiovascular and Comorbidity optimization) (Lip 2017) for the management of patients (Hindricks *et al.* 2021). This pathway has been shown to lower all-cause death, composite outcomes of stroke/major bleeding/CV death and first hospitalization (Proietti *et al.* 2018), as well as lower rates of CV events (Proietti *et al.* 2018) and reduced health-related costs (Pastori *et al.* 2019). Recent studies have shown a clear

beneficial role of early and systematic rhythm control strategy for all patients irrespective of symptoms (Willems *et al.* 2022), thereby underlining the need for early detection and active rhythm management using ablation and/or anti-arrhythmic drug therapies for these patients.

## 2.2. Central hemodynamics

HT is the most common modifiable risk factor for AF (Hindricks *et al.* 2021). Patients with HT have a 1.7-fold higher risk of AF development compared to normotensive patients (Lip *et al.* 2017). HT also plays an important role in the complications of AF as these patients have a higher stroke risk, and at the same time they are more susceptible to bleeding (Hindricks *et al.* 2021). BP assessment and HT treatment is an integral part of the management of patients with AF.

### 2.2.1. Central blood pressure

Traditionally to this day BP is measured at the brachial artery to diagnose and treat patients with HT or assess BP for screening of the disease. It has been widely accepted that the brachial artery pressure represents the systemic BP of the individual. However, notable differences can be seen at different sites of measurements (Avolio *et al.* 2009) due to the pulse pressure amplification (PPA) phenomenon. A substantial pressure difference between the peripheral and central arteries has been shown, reaching about 10–15 mmHg on average (O'Rourke and Adji 2010) and even up to 40 mmHg in some cases (Pauca *et al.* 2001; Ohte *et al.* 2007). Marked variations in aortic-brachial pressure differences are seen in healthy adolescents and in patients with CVD (O'Rourke *et al.* 2000).

The heart and the vasculature are closely intertwined. The vascular system receives blood ejected from the heart, but this is not only a passive function. Due to the “Windkessel” function, the vasculature is actively taking part in the redistribution of blood. In the systolic phase, the left ventricle generates a forward moving pulse wave. Because of branching of the arteries and increasing impedance in the resistance arteries a backward reflecting pulse wave is generated (McEniery *et al.* 2014). These two opposite travelling pulse waves make up the local waveform at any given site. The force that is exerted on the vascular walls can be divided into a pulsatile component (pulse pressure; PP) and a steady component (mean arterial pressure; MAP). The latter is determined by cardiac output (CO) and the vascular resistance, and the former is determined by heart rate (HR), left ventricular ejection fraction (EF), stiffness of the large arteries and pulse wave reflection (Vlachopoulos *et al.* 2011).

In large healthy conduit arteries, the backward moving wave reaches the heart in the diastolic phase, thereby increasing diastolic BP and enhancing coronary blood flow. Increased stiffness of these arteries accelerates the wave propagation (pulse wave velocity, PWV), thereby causing the reflected wave to merge with the incident wave in the systolic phase, augmenting the systolic BP and PP

(Williams 2004). The increase in systolic BP causes increased afterload in the left ventricle, which in turn increases oxygen consumption and leads to left ventricular hypertrophy and also affects other central organs like the brain, kidneys, and the large vessel walls. The impact of the reflected pulse wave on the merged wave can be quantified by the measurement of augmentation index (AIx), which can be assessed by pulse wave analysis (PWA) (Pauca *et al.* 2001; Van Bortel *et al.* 2001). The systolic BP is amplified when moving away from the aorta to the peripheral arteries due to PPA phenomenon, but the MAP and diastolic BP fall only by 1–2 mmHg. This small decrease is sufficient to move the blood forwards (Vlachopoulos and O'Rourke 2000). The pulsatile components of the central and peripheral pressures (systolic BP and PP) can vary substantially and the peripheral systolic blood pressure (pSBP) and peripheral pulse pressure (pPP) seem to overestimate the central systolic blood pressure (cSBP) and central pulse pressure (cPP), especially in younger adults who display a pronounced PPA (McEniery *et al.* 2005; Agabiti-Rosei *et al.* 2007; Vlachopoulos *et al.* 2011).

Since most organs rely on cBP, the assessment of cBP should be clinically more important and better estimate hypertension-mediated organ damage. The Strong Heart Study confirmed that cBP is a better predictor of CV events than pBP (Roman *et al.* 2007) in participants without clinical CVD at baseline. Similar results were confirmed in a meta-analysis by Vlachopoulos *et al.* (2010).

### 2.2.2. Assessment of central blood pressure

There are different methods available to assess cBP. The most direct method involves cardiac catheterization and direct recording of the BP in the ascending aorta with a pressure-sensing catheter. Because it is highly invasive, this method is not suitable for routine use in everyday clinical practice or the screening of large populations (Wilkinson *et al.* 2010).

Therefore, non-invasive methods have been developed to assess cBP using pressure waveform measurements from a distal site like the brachial, radial, or carotid arteries and calibration to the BP recorded by cuff sphygmomanometry (McEniery *et al.* 2014). Carotid artery pressure is sometimes used as a surrogate for aortic pressure due to its close proximity to the aorta. The carotid pressure waves are recorded using applanation tonometry and scaled to the brachial MAP and diastolic BP because these do not vary throughout the arterial vasculature (Kroeker and Wood 1955; McEniery *et al.* 2014). Because good quality pressure waveforms from the carotid artery can be hard to obtain, this method is highly operator-dependent. Also, it is likely that there is a small degree of amplification between the carotid artery and aorta, which may overestimate the cBP (Vlachopoulos *et al.* 2011; McEniery *et al.* 2014).

Non-invasive devices need to be calibrated to the brachial systolic and diastolic cuff pressures. These have been shown to underestimate the invasively measured brachial pressure, thereby leading to a lower estimate of cBP. However, data from recent studies have indicated that the errors in the estimation of cBP are equivalent to brachial cuff sphygmomanometry errors (Shih *et al.* 2011;

O'Rourke and Adji 2012). Devices using radial waveforms that are calibrated to the brachial pressures may even further underestimate the cBP because of brachial-to-radial amplification (Verbeke *et al.* 2005; Mahieu *et al.* 2010).

Newer devices have been developed that scale brachial waveforms obtained with pulse volume plethysmography to measure brachial cuff pressure. These negate the effects of brachial-to-radial amplification. These devices are less operator-dependent and seem to be better suited for clinical use (Weber *et al.* 2011; Sung *et al.* 2012).

### 2.2.3. The impact of antihypertensive medications on central blood pressure

There is a huge body of evidence that has shown beneficial effects of pBP reduction on all major CV events and all-cause mortality (Thomopoulos *et al.* 2014; Ettihad *et al.* 2016).

A reduction in cBP with antihypertensive drugs better predicts further CV events than pBP (Williams *et al.* 2006). There is evidence that supports that BBs have a smaller effect on cBP compared to other antihypertensive drugs where a reduction of both, cBP and pBP, was seen (Morgan *et al.* 2004; Mackenzie *et al.* 2009; McGaughey *et al.* 2016). Even when combination therapy with valsartan/amlodipine vs atenolol/amlodipine was used, the patient receiving a combination with BBs had smaller cBP reduction (Boutouyrie *et al.* 2010).

It must be noted that the class of BBs is diverse, and most studies have used atenolol as a study drug. Although bisoprolol seemed to have the same effect as atenolol (Deary *et al.* 2002), the inferior performance on cBP might not be a class effect. Studies with nebivolol, a vasodilating BB, reduced cBP, cPP, and left ventricular wall thickness significantly more than metoprolol, with comparable reduction in pBP and HR (Kampus *et al.* 2011). The superiority of nebivolol over atenolol in central pressure reduction was also confirmed by Dhakam *et al.* (Dhakam *et al.* 2008). There is some evidence that, through reducing HR, non-vasodilating BBs may be associated with augmentation of cBP, thereby reducing the lowering effects on cBP (Williams *et al.* 2006; Kampus *et al.* 2011).

The latest European Society of Cardiology (ESC) guidelines on HT (Williams *et al.* 2018) still recommend BBs for BP treatment as an option, but the evidence points to an inferior CV risk reduction compared to other major antihypertensive drug classes (Carlberg *et al.* 2004; Lindholm *et al.* 2005). The inferior efficiency was evident despite similar reduction in pBP (Williams *et al.* 2006).

## 2.3. Arterial stiffness

AS is a condition that affects the elasticity and compliance of the arterial walls, leading to an increased resistance to blood flow and a decreased ability to absorb the pressure changes caused by the cardiac cycle.

The structural components of the arterial wall, namely elastin and collagen, play an important role in AS (Laurent *et al.* 2003; Laurent *et al.* 2006; Townsend *et al.* 2015). These give the arterial wall its compliance and elasticity. The balance of these proteins in the vessel wall is stable because of constant production and breakdown. Situations that cause dysregulation of this constant state, like an inflammatory environment and OxS, lead to diminished production of elastin. The chronic increase in intraluminal pressure (e.g. HT) causes an upregulation of collagen production and thereby increases the stiffness of the vessel wall (Xu *et al.* 2000; Ziemann *et al.* 2005). Besides passive structural properties, functional components that are affected by endothelial function, like vessel wall smooth muscle tone or alterations of the integrity of the extracellular matrix, modify AS (Ziemann *et al.* 2005; Townsend *et al.* 2015).

Stiffening of the arteries is not evenly distributed throughout the vascular tree, occurring more in the central and conduit vessels while the peripheral arteries remain unaffected (Benetos *et al.* 1993; Gillessen *et al.* 1995; Ziemann *et al.* 2005). The stiffening of large arteries causes hemodynamic effects due to the rise of early aortic systolic pressure and increased blood pulse wave propagation (Chirinos *et al.* 2019). In the systolic phase of the cardiac cycle, the left ventricle needs to increase its pressure to generate a forward moving pulse to push blood into the aortic root. The amount of pressure needed is determined by the local impedance in the aortic root and is influenced by the aortic root stiffness and the diameter of the aorta. As the local impedance in the aorta is more affected by aortic diameter, then aortic stiffening is compensated by dilatation of the aortic root to decrease local impedance (Ziemann *et al.* 2005; Chirinos *et al.* 2019).

The left ventricle causes a pressure wave that is transmitted to the conduit arteries. This wavefront is partially reflected in different parts of the vascular tree, mostly in sites of impedance mismatch like bifurcations of the arteries or changes in the vessel wall composition. The reflected waves from different sites are conducted back to the aorta and merged. The timing of the reflected wave is strongly affected by the PWV of the conduit vessels. In younger patients or patients with slow PWV, the reflected pressure wave arrives at the aorta during diastole, increasing the diastolic pressure (Ziemann *et al.* 2005). Increased stiffness in the aorta causes the reflected pressure wave to move faster and arrive earlier. The reflected pressure wave arrives in mid or late systole, increasing systolic pressure amplification without diastolic pressure augmentation. This phenomenon is seen as the widening of the cPP. Measurements from the brachial artery may miss this or underestimate the increased cPP because the amplification is more pronounced in the central arteries than peripheral arteries, and not only peak systolic pressure is increased but also the morphology of the pressure waveform changes, which is

important in abnormal ventricular-vascular interaction (Laurent *et al.* 2006; Weber and Chirinos 2018; Chirinos *et al.* 2019).

Peak myocardial wall stress occurs at the early systolic phase. The left ventricle seems to be well adapted to deal with this pressure if no myocardial ischemia is present. At the same time, it is known that peak myocardial wall stress determines the oxygen consumption of the ventricle, and increased aortic impedance increases the myocardial oxygen demand, thereby reducing the left ventricular function in the presence of ischemia. The arrival of the reflected pulse wave during mid-to-late systole because of increased PWV causes increased systolic load and a decrease in diastolic pressure amplification, which reduces coronary blood flow and may diminish the coronary perfusion reserve (Zieman *et al.* 2005; Hoffman and Buckberg 2014; Chirinos *et al.* 2019). Studies have shown that increased late systolic load leads to left ventricular hypertrophy and fibrosis (Kobayashi *et al.* 1996; Hashimoto *et al.* 2008; Zamani *et al.* 2015) and impairs ventricular relaxation, leading to an increased risk of HF (Gillebert *et al.* 2000).

### 2.3.1. Clinical importance of arterial stiffness

Carotid-femoral PWV (cfPWV) is considered the “gold standard” method for AS measurement due to its relative ease of use and useability in large populations (Townsend *et al.* 2015). Different devices are available that use pressure sensors or ultrasound to detect the pulse waves. The signals can be obtained simultaneously or consecutively by using an ECG tracing and the peak of the QRS complex to calculate the time delay between the measurement sites (Townsend *et al.* 2015; Chirinos *et al.* 2019). Although PP is not directly a measure of AS, it has often been used as a surrogate marker of AS (Mackenzie *et al.* 2002).

There is substantial evidence that AS is a marker of CV risk (Vlachopoulos *et al.* 2010). AS has been found to be an independent predictor of primary coronary events (Boutouyrie *et al.* 2002) and stroke in hypertensive patients (Laurent *et al.* 2003). Accumulating data shows the importance of AS in processes leading to brain, kidneys, liver, placental, and even testicular damage (Chirinos *et al.* 2019). AS is the main determinant of increased PP, leading to increased systolic BP and causing isolated systolic HT (Safar 2018).

Studies indicate a reversibility of AS in response to drug therapy. Small and large arteries have been shown to be primary targets for antihypertensive therapy. There is data showing that ACEIs, ARBs and mineralocorticoid receptor antagonists may modify the collagen content of the arterial walls independently of BP lowering (Van Bortel *et al.* 2001). These findings indicate a new potential target besides BP reduction for better CV risk reduction.

## 2.4. Role of central blood pressure and arterial stiffness in the development of atrial fibrillation

The pathophysiological mechanisms leading to AF are complex and to this date not fully understood. AF is caused by an interaction of common CV risk factors with genetic and age-related changes that lead to structural and functional changes in the atria (Hindricks *et al.* 2021). It has been well established that left atrial (LA) size is a known risk factor for new-onset AF and reoccurrence (Vaziri *et al.* 1994; Tsang *et al.* 2001; Parkash *et al.* 2004; Bang *et al.* 2013; Sardana *et al.* 2018). LA size seems to be a stroke risk factor even in the absence of AF (Overvad *et al.* 2016).

Studies on central hemodynamics and AS have shown that PWV and PP, a surrogate marker for AS, is correlated with LA size in hypertensive patients without previous AF episodes (Lantelme *et al.* 2008). This was also confirmed by another small study with hypertensive patients (Janwanishstaporn and Boonyasirinant 2016) and by a larger prospective, community-based observational study where pPP was predictive of AF incidence (Mitchell *et al.* 2007). These results demonstrate that increased AS may cause atrial enlargement, a known risk factor for AF (Vaziri *et al.* 1994; Tsang *et al.* 2001; Parkash *et al.* 2004).

Aortic stiffening causes the early arrival of the reflected pulse wave, causing an increase of the late cSBP (Chirinos *et al.* 2017). An increase in late systolic load has been associated with left ventricular diastolic dysfunction (Chirinos *et al.* 2017). The LA plays an important role in the filling of the left ventricle and acts not only as a conduit but also a booster to facilitate the rapid diastolic filling. In the early stages of HT, the conduit function of the LA decreases, but the booster function seems to increase (Eshoo *et al.* 2009). In the later stages of HT, the booster function is also impaired, leading to an increased risk of HF development and a worse prognosis (Soullier *et al.* 2016). Late systolic load has been associated with an increased risk of left ventricular remodeling and more fibrosis. This may increase the diastolic stiffness of the left ventricle that leads to higher atrial load, causing LA dilatation and dysfunction (Kobayashi *et al.* 1996; Ellims *et al.* 2014), further promoting AF development. Newer studies looking at cBP and cPP have confirmed that functional changes in the LA may develop even before structural changes can be identified (Przewłocka-Kosmala *et al.* 2019), and increases in cBP and AS might provide a pathophysiological link to the development of AF.

## 2.5. Markers of fibrosis, inflammation, and oxidative stress in patients with atrial fibrillation

The natural progression of AF causes the arrhythmia to develop from a paroxysmal self-limiting form to a more persistent disease that needs medical interventions. The end-stage of the disease is permanent AF. A lot of individual variability is seen in the progression, and this seems to be affected by a combination of risk factors and treatment (Hindricks *et al.* 2021).

Many risk factors have been established that correlate with disease progression, such as older age, male sex, HT, CAD, HF and valvular heart disease, but also inflammatory heart disease. Also, extracardiac factors like hyperthyroidism and sleep apnea, kidney diseases, obesity, and alcohol consumption are related to advanced stages of AF (Vlachos *et al.* 2016).

Investigations in the mechanisms that lead to advanced stages of AF are important to better understand the disease and develop strategies to better estimate the prognosis of the individual patient and propose patient-tailored treatment strategies. Studies on the molecular and structural mechanisms of AF have associated inflammatory, fibrotic (Guo *et al.* 2012; Hu *et al.* 2015), and oxidative processes (Korantzopoulos *et al.* 2007; Samman Tahhan *et al.* 2017; Korantzopoulos *et al.* 2018; D’Oria *et al.* 2020) with the development and progression of the disease. The role of different biomarkers related to AF has been of great research interest to better quantify the individual disease stage and choose a suitable treatment strategy.

### 2.5.1. High-sensitive C-reactive protein

High-sensitive C-reactive protein (hsCRP) is, as the name suggests, a more sensitive marker for inflammation than the routinely used C-reactive protein (CRP) (Bassuk *et al.* 2004). Recent research suggests that chronic inflammation can alter atrial electrophysiology and increase vulnerability to AF (Hu *et al.* 2015). The Cardiovascular Health Study, a large prospective cohort study (Aviles *et al.* 2003), and others (Marott *et al.* 2010), have shown that CRP is associated with presence of AF, and hsCRP (Rizos *et al.* 2010) can also predict development of new-onset AF.

Interestingly, it is not clear if inflammation is a consequence or the cause of AF. The first information on the role of inflammation in the occurrence of AF came from patients with inflammatory states like pericarditis, myocarditis, and cardiac surgeries, where AF was frequently seen (Bruins *et al.* 1997; Amar *et al.* 2004). The Women’s Health Study confirmed the independent association of inflammatory biomarkers, amongst others CRP, with incidence of AF in healthy women during an almost 15-year follow-up (Conen *et al.* 2010).

It has been also suggested that AF *per se* can maintain the inflammatory response and play a role in atrial remodeling (Korantzopoulos *et al.* 2018). Patients with successful ablation had a decline in CRP levels compared to those without

success, demonstrating the potential role of AF in upholding the inflammatory response (Rotter *et al.* 2006).

Inflammatory markers also seem to have a prognostic effect on treatment outcomes.

The success of electrical cardioversion and the risk of recurrence has been independently associated with levels of hsCRP (Watanabe *et al.* 2006). These results were also confirmed in a meta-analysis by Yo and colleagues (Yo *et al.* 2014). HsCRP also seems to correlate with the success of AF ablation in some studies (Henningsen *et al.* 2009).

There is evidence that inflammation can have a triggering effect on AF and at the same time create a sustainable environment for the arrhythmia. This can cause a vicious circle that contributes to the progressive nature of AF.

### 2.5.2. Galectin-3

Galectin-3 (Gal-3) is a protein that belongs to the lectin family and is involved in cell differentiation, fibrinogenesis and inflammatory processes (Dong *et al.* 2018). Gal-3 promotes fibrosis by activating (myo)fibroblasts and endocardial cells (Henderson and Sethi 2009). Studies have shown Gal-3's role in the acute phase of the inflammatory response by activating mast cells and neutrophils. Gal-3 has also been linked to the transition from acute to chronic inflammation by causing fibrogenesis and tissue fibrosis (Henderson and Sethi 2009). Several studies have provided new insight into associations between Gal-3 and AF, and a link with incident episodes of arrhythmia was seen in a population without previous history of the disease (Ho *et al.* 2014; Fashanu *et al.* 2017).

Besides involvement in the initiation of the arrhythmia, Gal-3 has been linked to disease progression. This has been shown in a study by Wang *et al.* (2021), where they witnessed constantly higher Gal-3 values in patients who progressed from paroxysmal forms to persistent AF.

A recently published meta-analysis (Zhang and Wu 2019) considered Gal-3 to be a predictor of AF ablation outcomes. The pooled findings showed higher levels of Gal-3 in patients with recurrent AF after ablation, and the association was independent of age, gender and LA dimensions.

### 2.5.3. Myeloperoxidase

Myeloperoxidase (MPO) has been shown to play a crucial role in the interaction between inflammation and OxS, leading to cardiac fibrosis (Ndrepepa 2019). MPO is an enzyme that is mostly released by activated polymorphonuclear neutrophils (Friedrichs *et al.* 2012) which leads MPO to be secreted into the extracellular environment of the tissue. MPO is then oxidized, after which it reacts with different molecules, resulting in the generation of reactive oxygen species (Friedrichs *et al.* 2012). MPO causes the production of different hypohalous acids, most notably hypochlorous acid (HOCl), which has been shown to activate matrix

metalloproteinases (MMPs) and to inactivate tissue-inhibitors of MMP (Ndrepepa 2019). These processes, among others, lead to increased extracellular matrix (ECM) turnover, collagen accumulation and fibrosis in the atrial tissue (Friedrichs *et al.* 2012). MPO has been associated with various CVDs (Ndrepepa 2019), but the link to AF is not so well established. Only a few clinical studies have dealt with the role of MPO in association with AF. According to Li and colleagues (Li *et al.* 2013), higher levels of MPO might be predictive of arrhythmia recurrence after AF ablation. A more recent study by Holzwirth *et al.* (2020) including 23 patients with AF during pulmonary vein isolation (PVI) found elevated MPO levels compared to controls but no differences in baseline MPO, irrespective of rhythm outcome. Interestingly, tenfold higher MPO levels were seen from blood samples taken from the LA than from the peripheral vein, indicating a direct origin from the LA. These findings seem to correlate with a study looking at perioperative AF, where patients with AF had higher levels of MPO in the blood and pericardial fluid than patients that remained in sinus rhythm after coronary artery bypass graft surgery (Liu *et al.* 2022).

#### 2.5.4. Oxidized low-density lipoprotein

The role of non-physiological OxS in the pathophysiological mechanisms leading to AF is an increasingly studied topic. Non-physiological OxS seems to play an important role in the LA remodeling process (Korantzopoulos *et al.* 2003). Mihm *et al.* (2001) were the first to show a marked elevation of OxS markers in their studies with chronic AF patients undergoing the Maze procedure.

Rapid atrial pacing is shown to induce a decrease in tissue levels of vitamin C, which is associated with increased protein nitration, a marker of increased OxS. These changes were also related to other electrophysiological changes like the decrease in the atrial effective refractory period that is seen in atrial electrical remodeling (Carnes *et al.* 2001).

Several different markers of OxS have been associated with AF (Samman Tahhan *et al.* 2017), but information on the role of oxidized low-density lipoprotein (oxLDL) is still limited. In a small study (Polovina *et al.* 2015), oxLDL was higher in patients with AF without other risk factors and was associated with development of HT. OxLDL has also been shown to correlate strongly with LA size in AF patients (Tousoulis *et al.* 2009).

#### 2.5.5. N-terminal pro-brain natriuretic peptide

B-type natriuretic peptide (BNP) and its non-active and more stable form N-terminal pro-brain natriuretic peptide (NT-proBNP) are well known in the diagnosis of HF, but their role in AF is not so well established. The hormone is released in response to increased wall stress in the heart, which is usually caused by increased loading conditions. In AF patients, the increase of NT-proBNP can be due to atrial volume overload but a high frequency of atrial contractions and local atrial inflammation has also been suggested as a cause (Möllmann *et al.* 2008).

The elevation of natriuretic peptides has also been seen in patients with other inflammatory states without AF, suggesting a potential common pathophysiological mechanism (Fish-Trotter *et al.* 2020). The elevation of NT-proBNP seems to be also associated with the degree of fibrosis of the atria in patients with AF (Hwang *et al.* 2009) and relates to serum markers of collagen turnover (Ravassa *et al.* 2015).

Population-based studies looking at the predictive role of NT-proBNP have shown that NT-proBNP levels can be used to predict new-onset AF irrespective of the other risk factors of AF (Asselbergs *et al.* 2008). The levels of the marker were also increased in patients with a history of AF who developed new episodes during a one-year follow-up in a recent study (Staszewsky *et al.* 2021).

Also, two published meta-analyses have demonstrated that NT-proBNP correlates well with the recurrence rate of AF after ablation (Zhang *et al.* 2016) and also electrical cardioversion (Xu and Tang 2017). These studies suggest that NT-proBNP could be a useful marker to assess the progression and prognosis of the arrhythmia.

## **2.6. Anticoagulation in patients with atrial fibrillation**

### **2.6.1. Stroke in patients with atrial fibrillation**

Stroke is the second highest cause of death worldwide after CAD. It is also the second largest cause of long-term disability (World Health Organisation 2023). It is estimated that about 50% of patients with stroke have reduced mobility and 26% remain disabled in basic activities of daily living (Katan and Luft 2018; Migdady *et al.* 2021). Many risk factors for stroke are modifiable, so the risk can be decreased substantially (O'Donnell *et al.* 2010).

AF increases stroke risk fivefold, and in 2 to 5% of patients ischemic stroke or a transient ischemic attack (TIA) is the first manifestation of the arrhythmia (Lubitz *et al.* 2017; Hindricks *et al.* 2021). Strokes in patients with AF or ischemic heart disease are related to a higher treatment cost (Go *et al.* 2014).

AF causes impaired contractions of the atria and reduces atrial emptying. This causes blood stasis and thrombogenesis and increases the risk of thromboembolism. Some studies have shown that rapid atrial pacing may decrease the production of nitric oxide (NO), which downregulates the expression of plasminogen activator inhibitor 1 (PAI-1), a prothrombotic protein. The resultant increase in PAI-1 may increase stroke risk (Cai *et al.* 2002). Atrial tissue samples have shown myofibrillar oxidative damage and fibrosis, which may further contribute to the increased thromboembolic state (Frustaci *et al.* 1997; Mihm *et al.* 2001).

Interestingly, some studies have revealed that atrial cardiomyopathy may increase thromboembolism risk even without the diagnosis of AF, indicating common underlying pathophysiological changes in the atria that lead to thromboembolism and AF (Kamel *et al.* 2014; Kamel *et al.* 2015; Yaghi *et al.* 2016).

### 2.6.2. Stroke risk assessment

Although stroke risk is generally increased in AF patients, it is not the same in all patients. Depending on specific factors and modifiers, the stroke risk can vary substantially (Hindricks *et al.* 2021).

Various widely known risk factors for stroke have been identified in patients with AF: age, HT, previous stroke, TIA, systemic embolism, structural heart disease, diabetes mellitus, vascular disease, HF, and female sex as a modifier (Pisters *et al.* 2012; Hindricks *et al.* 2021). Besides these, other imaging-related markers, blood or urine markers, and clinical risk factors have been established (Szymanski *et al.* 2015).

Stroke risk scores have been developed to better assess the individual risk of a patient. These scores need to be usable in everyday clinical practice but should also be precise (Rivera-Caravaca *et al.* 2017). To date, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score is mostly used for stroke risk assessment in AF patients (January *et al.* 2019; Hindricks *et al.* 2021). This score can identify patients who have a very low stroke risk and do not need any preventive therapy, but it is only moderately able to predict the very high-risk patients who will have a thrombo-embolic event (Hindricks *et al.* 2021).

Other risk scores, such as the GARFIELD-AF risk score (Fox *et al.* 2017) and scores including biomarkers like ABC-stroke (Hijazi *et al.* 2016; Benz *et al.* 2021) and ATRIA (Zhu *et al.* 2017), have been developed to improve risk stratification. Although studies have shown superiority to the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, these have not yet been adopted into everyday clinical practice, most likely due to their increased cost and difficulty of use.

According to the ESC guidelines on AF, stroke preventive therapies should be initiated in patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$  in men and  $\geq 3$  in women. It should be considered for patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 in men and 2 in women, and therapy is not recommended in low stroke risk patients with a score of 0 in men and 1 in women (January *et al.* 2019; Hindricks *et al.* 2021). The Estonian AF Guidelines recommend anticoagulation therapy for stroke prevention in patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$  (Eesti Haigekassa Ravijuhendite nõukoda 2018).

### 2.6.3. Prevention of stroke risk

OAC therapy is the cornerstone of stroke prevention. The two main options are vitamin K antagonists (VKA) or the use of NOACs.

VKAs (mostly warfarin) have long been used for stroke prevention. They have shown the ability to reduce stroke risk by 64% and decrease the mortality rate by 26% (Hart *et al.* 2007) compared to placebo in AF patients. They are still used worldwide due to their low cost.

There are known problems that hinder their effective and widespread use: VKAs have a long onset and offset, a narrow therapeutic window, and interactions with food and other drugs. The dosing needs to be individualized and adjusted

according to the international normalized ratio (INR) (Dalby *et al.* 2013; De Caterina *et al.* 2013). In AF patients, the recommended INR should be between 2.0–3.0 (Hindricks *et al.* 2021). The quality of treatment with VKAs is assessed by calculating the INRs time in therapeutic range (TTR), where a percentage of >70% is considered adequate (Ababneh *et al.* 2021).

Because of the aforementioned problems with VKAs, NOACs have been developed. Trials with the available NOACs have shown to be non-inferior to warfarin in the prevention of stroke and systemic embolism (Connolly *et al.* 2009; Granger *et al.* 2011; Patel *et al.* 2011; Giugliano *et al.* 2013). Compared to warfarin, a 19% reduction in stroke and systemic embolism risk was seen, as well as a 51% reduction in hemorrhagic stroke and a further 10% decrease in all-cause mortality, with an overall better safety profile for bleeding (Ruff *et al.* 2014). As these drugs have clear dosing/dose-reducing suggestions and a good efficacy and safety profile without the need for INR monitoring, they are recommended as the preferred option for most patients, except patients with mechanical heart valves or moderate-to-severe mitral stenosis (January *et al.* 2019; Hindricks *et al.* 2021; Steffel *et al.* 2021).

In a small population of patients, left atrial appendage (LAA) occlusion devices or the surgical removal of the LAA can be used to reduce the stroke risk if long-term use of OACs is contraindicated (Hindricks *et al.* 2021). A study looking at AF patients with high stroke and bleeding risk found that LAA occlusion with a device was non-inferior to NOAC therapy regarding the composite endpoint (stroke, TIA, systemic embolism CV death, major and non-major clinically relevant bleeding and procedure-/device-related bleeding) during a median follow-up of almost 20 months (Osmancik *et al.* 2020). The recently published follow-up data of four years confirmed the long-term non-inferiority to NOACs in this patient population with a significant reduction of non-procedure related bleeding events (Osmancik *et al.* 2022).

#### **2.6.4. Adherence, treatment persistence, and its prognostic impact**

With a wide availability of NOACs that do not need frequent monitoring, concerns have been raised about the long-term persistence (Cramer *et al.* 2008) of OAC therapy in patients with AF.

Data from registries like GARFIELD-AF and ORBIT-AF II have shown OAC use in 69% and 87% of the patients with  $CHA_2DS_2-VASc \geq 2$ , respectively (Steinberg *et al.* 2017; Bassand *et al.* 2021). Coinciding with the data from the registries, studies show that about 25–35% of high-risk patients still do not use OACs (Lowres *et al.* 2019).

Data on the persistence of OAC therapy and its association with clinical outcomes varies, as does the definition of persistence in different studies. Older data looking at warfarin use has shown a discontinuation rate from 26% to 55% at one year (Fang *et al.* 2010; Spivey *et al.* 2015). Recent studies with NOACs have shown

real-world discontinuation rates ranging from 16% to 53% (Beyer-Westendorf *et al.* 2016; Paquette *et al.* 2017; Raparelli *et al.* 2017), and during clinical trial follow-up rates from 21% to 34% (Connolly *et al.* 2009; Granger *et al.* 2011; Patel *et al.* 2011; Giugliano *et al.* 2013) were seen during a 6- to 24-month period.

The ORBIT-II registry showed a discontinuation rate of 13% in patients taking warfarin and 15% in those on NOAC therapy after a one-year period. Discontinuation was associated with increased absolute risk of all-cause mortality and CV death (Jackson *et al.* 2020). Similarly, the GARFIELD-AF registry saw that 13% of patients discontinue their OAC treatment after a median follow-up of 511 days, defined as cessation of treatment for  $\geq 7$  consecutive days. This was associated with significantly higher all-cause mortality, MI, and stroke or systemic embolism risk. Substantial differences in discontinuation rates were seen between countries (Cools *et al.* 2021)

There are no registries that include data about OAC use in Estonia, so systemic information about OAC use persistence is needed.

## 2.7. Summary of the literature review

AF is a common arrhythmia in clinical practice, but the pathophysiological mechanisms and hemodynamic changes leading to the fibrosis of LA and the development of AF are not yet fully understood. Several risk factors for this arrhythmia are known, such as diabetes, sleep apnoea, and obesity. HT related mechanisms seem to play a major role in the processes leading to the arrhythmia. Biomarkers have been of great interest to better understand the progression of AF and estimate the severity of the disease. Some studies have also suggested a potential benefit of biomarkers in choosing the best individual treatment strategies. AF significantly impairs the patient's quality of life and increases the risk of stroke by up to 5 times. Most  $\geq 65$ -year-old patients with AF are considered at a high stroke risk, leading to the need of lifelong continuous anticoagulant therapy. Although highly effective, worldwide registries indicate a constant underuse of these drugs. Data about OAC use in Estonia for stroke prevention is lacking but is much needed.

### 3. AIMS OF THE THESIS

The general purpose of this thesis was to study the biochemical and hemodynamic changes in patients with atrial fibrillation, as well as to assess the current state of anticoagulation of  $\geq 65$ -year-old atrial fibrillation patients in Estonia.

Specific aims:

1. To evaluate central blood pressure in patients with atrial fibrillation compared to controls.
2. To assess pulse wave velocity as a marker of arterial stiffness in atrial fibrillation patients compared to controls.
3. To determine the serum levels of inflammatory, fibrotic, and oxidative stress markers and evaluate their association with atrial fibrillation compared to the control group.
4. To assess the association of markers of inflammation, fibrosis and oxidative stress with atrial fibrillation recurrence rate during a one-year follow-up.
5. To describe the antithrombotic treatment trends of patients with atrial fibrillation aged  $\geq 65$  years in Estonia during 2019 and 2020.
6. To study the relationship between anticoagulation lifestay coverage and one-year survival in patients with atrial fibrillation aged  $\geq 65$  years during 2019 and 2020.

## **4. SUBJECTS AND METHODS**

### **4.1. Study population**

#### **4.1.1. Paper I**

Paper I: The study population consisted of patients with paroxysmal or persistent AF (n=76) who were hospitalized for cardioversion or PVI. Patients were recruited from the Department of Cardiology, Tartu University Hospital, and the Centre of Cardiology, North Estonia Medical Centre, Estonia, respectively.

The inclusion criteria were as follows: aged 18–75 years, successful cardioversion to sinus rhythm (SR) or SR before the PVI procedure.

The exclusion criteria were the following: contraindication for cardioversion or unsuccessful procedure, any comorbid acute or chronic inflammatory disease, known moderate to severe valve pathology, HF, or malignancy.

The control group consisted of 75 age-matched subjects with no previous history of AF or any other known arrhythmia. The control subjects were recruited from family doctors' practices. The same exclusion criteria were followed as with study patients: known acute or chronic inflammatory disease, diagnosis of HF, previously diagnosed malignancy or moderate to severe valve pathology.

#### **4.1.2. Paper II**

Paper II: The study population consisted of patients with paroxysmal or persistent AF (n=75) who were hospitalized for cardioversion or PVI. Patients were recruited from the Department of Cardiology, Tartu University Hospital, and the Centre of Cardiology, North Estonia Medical Centre, Estonia, respectively.

The the same inclusion and exclusion criteria were used as in paper I. The inclusion criteria were: aged 18–75 years, successful cardioversion to SR or SR before the PVI procedure.

The exclusion criteria: contraindication for cardioversion or unsuccessful procedure, any acute or chronic comorbid inflammatory disease, malignancy, HF or known moderate to severe valve pathology.

The control group was compromised of 75 age-, sex-, and BP-matched subjects with no previous history of AF or any other known arrhythmia. The control subjects were recruited from family doctors' practices. The same exclusion criteria were followed as with study patients: known acute or chronic inflammatory disease, diagnosis of HF, previously diagnosed malignancy or moderate to severe valve pathology.

### 4.1.3. Paper III

The study population consisted of two cohorts of patients with documented diagnoses of AF (I48, International Statistical Classification of Diseases 10th revision [ICD-10]) aged  $\geq 65$  years from the year 2018 and alive as of 01.01.2019 (cohort I,  $n=34,018$ ) and patients with a new AF documentation from the year 2019 and alive as of 01.01.2020 (cohort II,  $n=9,175$ ). The list of patients that matched the inclusion criteria was obtained from the Estonian Health Insurance Fund's (EHIF) database.

## 4.2. Study design and protocol

### 4.2.1. Papers I and II

This was a two-centre, prospective, controlled clinical trial. The medical and lifestyle history was collected from all participants. Height and weight were assessed, and body mass index (BMI) was calculated. Venous blood samples were collected from the antecubital fossa after an overnight fast. BP, cfPWV and PWA measurements were performed within one day in patients after successful restoration of SR with cardioversion. Measurements of BP, PWV and PWA were made before the procedure in patients who were hospitalized for PVI. All measurements were performed after 15 minutes of rest in a quiet, dedicated temperature-controlled room in a supine position. All patients were in SR during the hemodynamic measurements.

A signed informed consent was obtained from all participants. The study was approved by the Research Ethics Committee of the University of Tartu (protocol nr 253/T-3) and was conducted in accordance with the Declaration of Helsinki.

### 4.2.2. Paper III

The EHIF database was used to create a list of patients matching the inclusion criteria by an EHIF analyst. Additional information about concomitant diseases for the same patients as classified by the ICD-10 were also obtained. The studied diseases were as follows: cancer (C00-C97), diabetes (E10, E11), HT (I10-I15), CAD (I21, I22, I25.2), stroke (I63, I64, I69.3), PAD (I70.2), renal insufficiency (N17-N19), and coronary stent (Z95.5).

Data about prescribed OACs for the period (01.01–31.12.2019 for cohort I and 01.01–31.12.2020 for cohort II or until death, if earlier) was acquired from the nationwide Estonian Medical Prescription Centre for the same patients.

The obtained data was linked to the Estonian Causes of Death Registry to establish the date of death. All-cause mortality rates by age and sex distribution were also obtained from the Estonian Causes of Death Registry to establish the baseline mortality rate for the whole Estonian population aged  $\geq 65$  years for the years 2019 and 2020. The personal information was removed, and a unique study code was assigned for every patient before release for analysis.

For lifeday coverage (LDC) analysis, daily doses of OACs recommended for stroke prevention were used as follows: warfarin (3 mg or 5 mg once a day [OD]) rivaroxaban (15 mg or 20 mg OD), apixaban (2.5 mg or 5 mg twice a day [BD]), dabigatran (110 mg or 150 mg BD) and edoxaban (30 mg or 60 mg OD). In case dosing was different, patients were categorized into the 0% group of OAC lifeday coverage. No data about INR was available in patients who used warfarin, therefore we considered dosing to be correct when at least 3 mg or 5 mg were used.

Individual informed consent to participate in this study was not obtained in accordance with the Estonian Personal Data Protection Act and the agreement from Research Ethics Committee of the University of Tartu. The study was approved (protocol nr 341/T-7) by the Research Ethics Committee of the University of Tartu and was conducted in accordance with the Declaration of Helsinki.

### **4.3. Methods**

#### **4.3.1. Brachial blood pressure measurement**

Papers I and II: brachial BP was measured in a supine position after at least 15 minutes of rest from the non-dominant arm in a dedicated study room. Measurements were performed with a validated digital oscillometric device (A&D UA-767; A&D Company Ltd., Tokyo, Japan). At least two readings were performed, and mean of readings was used in further analysis.

#### **4.3.2. Assessment of aortic pulse wave velocity**

Papers I and II: arterial stiffness was assessed using cfPWV. Simultaneous waveforms from the carotid artery and femoral artery were measured with Sphygmocor XCEL (AtCor Medical, Sydney, Australia). The femoral waveform was recorded by a partially inflated cuff, controlled by the machine. Carotid waveforms were recorded using applanation tonometry. At least two cfPWV measurements were performed and the mean values were used for analysis. The maximal difference of 0.5 m/s was allowed, otherwise a third measurement was performed and the two closest values were used to calculate the mean. The quality of the measurements was controlled using the built-in quality control indicator. These were repeated if they did not meet the quality requirements.

#### **4.3.3. Pulse wave analysis**

Paper I: The brachial pulse wave was used for PWA measurement. Central aortic waveforms were obtained and PWA was assessed using SphygmoCor Brachial generalized transfer function (GTF). AIx, augmentation index corrected for a heart rate of 75 beats/minute (AIx@75), cPP, cSBP, augmentation pressure (AP), and MAP were provided. The AIx was defined as the ratio of cPP and the reflected augmentation pressure from the central aortic waveform (Laurent *et al.* 2006). PPA was defined as the ratio of pPP to cPP ( $PPA = pPP / cPP$ ) (Pichler *et al.* 2016).

At least two measurements were performed, and the mean value was used for the analysis. If the difference between measurements was more than two units, then a third measurement was made and the mean value of the two closest measurements was used.

#### **4.3.4. Echocardiography**

Paper I: Echocardiography was performed as part of the routine clinical management of the study patients by experienced personnel in this field. The echocardiographic information was available for all AF patients who were scheduled for cardioversion or PVI procedure and for 29 patients from the control group.

#### **4.3.5. Laboratory analysis**

Papers I and II: Venous blood samples were collected after an overnight fast in the morning of the procedures. The analysis of complete blood count, hsCRP, CRP, creatinine, estimated glomerular filtration rate (eGFR), plasma glucose levels, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides and NT-proBNP were analyzed in the United Laboratories of Tartu University Hospital or in the North Estonian Medical Centre laboratory using standard commercially available assays.

Paper II: For the analysis of Gal-3, MPO and oxLDL, blood samples were centrifuged and serum extracted and stored at  $-80^{\circ}\text{C}$ . The analysis was performed in the laboratory of the Department of Biochemistry, University of Tartu. Gal-3 was measured using the ARCHITECT Gal-3 assay kit, employing chemiluminescent microparticle immunoassay technology. MPO was measured using the BIOCHECK MPO enzyme immunoassay kit, and oxLDL was measured using the MERCODIA oxLDL kit, both by employing enzyme-linked immunosorbent assay technology.

#### **4.3.6. Follow-up**

Paper II: After successful cardioversion or PVI, the patients were monitored using ECG telemetry for at least a day. Patients were scheduled for a follow-up visit at 3–4 months, six months and one year after electrical cardioversion to detect AF recurrence. Standard 12-lead ECGs were obtained at each visit, and patients were questioned about rhythm disturbances. For patients after PVI, a Holter monitoring was performed three months after the procedure. Electronic medical records were used to follow the patient remotely for any documentation of rhythm disturbances. The endpoint was documentation of new AF episodes during follow-up with ECG or complaints of arrhythmias.

Electronic medical records were also used for the remote follow-up of the control group for one year. Electronic medical records, ECGs and family physicians' electronic notes were checked for the diagnosis of AF.

Maintenance of SR was defined as successful if we saw no documentation of AF on ECG or a 24-hour Holter during the period or absence of medical contact because of rhythm disturbances.

#### 4.3.7. Statistical analysis

Paper I: The groups were compared using the chi-squared test on categorical variables and the Student's t-test on continuous variables. For the assessment of linear relationships between continuous variables, the Pearson's correlation was used. P-values  $< 0.05$  were considered statistically significant.

Multiple linear regression analyses were performed to investigate the associations of cPWV and PPA on a set of predictors. Samples with any missing data were excluded from the analysis, and the models were adjusted for potential confounders like age and sex. The analysis was performed with statistical program R (R Core Team 2020), version 3.6.3.

Paper II: Continuous variables were compared using Student's t-test, and categorical variables were compared using the chi-squared test.

All variables of univariate analyses with p-value  $< 0.1$  were included in the multivariable logistic regression model, and backward elimination was used for variable selection to identify independent risk factors for the association with AF. Statistical significance was defined as a p-value  $< 0.05$ . All statistical analyses were performed using R (R Core Team 2020), version 3.6.3.

Paper III: The means and standard deviations (SD) were used to present continuous variables, while frequencies and percentages were used for categorical variables.

LDC was defined as the proportion of days alive that are covered by a OAC dose, that is recommended for stroke prevention. LDC was calculated for one year, but also prescriptions from the previous year were considered that overlapped with the study period. If the patient was prescribed another OAC during the period, then the prescription date was used as the switching day and any remaining doses from the previous drug were excluded from the LDC calculation.

To compare the LDC groups of OACs, the Student's t-test was used for continuous variables, while the chi-squared test was used for categorical variables.

All-cause mortality was assessed using the Kaplan-Meier method, and differences between groups were tested by the log-rank test. Age-, sex-, and calendar year-matched general Estonian population data was used to estimate the expected survival. Relative survival was calculated to estimate disease-specific survival as the ratio of the observed all-cause survival of all the patients to the expected all-cause survival in the general population (Ederer *et al.* 1961).

An underlying assumption of relative survival is that deaths associated with, or due to AF are an insignificant proportion of all deaths. Relative survival was estimated using the Pohar Perme non-parametric method, implemented in R package 'relsurv' (Perme *et al.* 2012), and survival curves were compared using a log-rank type test (Grafféo *et al.* 2016). Statistical analyses were performed using R (R Core Team 2020), version 4.2.1.

## **5. RESULTS**

### **5.1. Association of atrial fibrillation with central blood pressure and arterial stiffness (Paper I)**

#### **5.1.1. Characteristics of the study population**

The general characteristics of the patients and control group are described in Table 1. No differences in age or height were seen. Patients in the AF group had bigger BMI ( $p < 0.001$ ). There were more men in the AF group (72% vs 51%,  $p = 0.010$ ).

Patients with AF had lower eGFR ( $p = 0.037$ ) and HDL ( $p < 0.001$ ), but higher creatinine ( $p = 0.001$ ) and CRP ( $p = 0.003$ ). Both groups had similar total cholesterol, LDL, and triglyceride values.

**Table 1.** Baseline clinical characteristics of the study group and the control group.

<b>Variable</b>	<b>AF group (n=76)</b>	<b>Control group (n=75)</b>	<b>p-value</b>
Age, years	57 (±9)	54 (±11)	0.064
Male sex, n (%)	55 (72)	38 (51)	0.010
Height, cm	175 (±10)	172 (±10)	0.778
Weight, kg	90.2 (±16.5)	76.3 (±16.1)	<0.001
Body mass index, kg/m <sup>2</sup>	29.4 (±4.7)	25.3 (±4.7)	<0.001
Peripheral systolic blood pressure, mmHg	127 (±13)	123 (±13)	0.131
Peripheral diastolic blood pressure, mmHg	78 (±9)	76 (±8)	0.142
Peripheral pulse pressure, mmHg	48 (±9)	47 (±9)	0.365
Central systolic blood pressure, mmHg	118 (±14)	114 (±12)	0.033
Central diastolic blood pressure, mmHg	79 (±9)	77 (±8)	0.179
Central pulse pressure, mmHg	39 (±9)	37 (±8)	0.035
Central mean arterial pressure, mmHg	94 (±10)	91 (±9)	0.101
Pulse pressure amplification	1.24 (±0.14)	1.30 (±0.13)	0.015
Systolic blood pressure amplification	1.07 (±0.04)	1.09 (±0.04)	0.039
Heart rate, beats per minute	58 (±9)	61 (±7)	0.076
Augmentation pressure, mmHg	12 (±6)	9 (±5)	0.001
Augmentation index, %	29 (±11)	23 (±12)	0.006
Augmentation index at heart rate of 75 beats per minute, %	21 (±11)	18 (±13)	0.085
Pulse wave velocity, m/s	8.0 (±1.2)	7.2 (±1.2)	<0.001
Diagnosis of hypertension, n (%)	49 (65)	2 (3)	<0.001
Use of beta blockers, n (%)	68 (90)	0 (0)	<0.001
Use of ACEIs, ARBs, n (%)	41 (54)	1 (1)	<0.001
Estimated glomerular filtration rate, mL/min/1.73 m <sup>2</sup>	83 (±15)	88 (±13)	0.037
Creatinine, µmol/L	84 (19)	75 (13)	0.001
C-reactive protein, mg/L	2.47 (±3.52)	1.08 (±1.21)	0.003
Total cholesterol, mmol/L	5.46 (±1.10)	5.39 (±1.06)	0.700
HDL-cholesterol, mmol/L	1.41 (±0.46)	1.67 (±0.45)	<0.001
LDL-cholesterol, mmol/L	3.70 (±1.04)	3.68 (±0.79)	0.866
Triglycerides, mmol/L	1.52 (±0.70)	1.34 (±0.75)	0.145

Values are presented as mean ± SD or count (%). SD – standard deviation; AF – atrial fibrillation; ACEIs – angiotensin-converting enzyme inhibitors; ARBs – angiotensin II receptor blockers; HDL – high-density lipoprotein; LDL – low-density lipoprotein

### 5.1.2. Comparison of the hemodynamic profile

Patients in the AF group had higher cfPWV (8.0 m/s vs 7.2 m/s,  $p<0.001$ ), cSBP (118 mmHg vs 114 mmHg,  $p=0.033$ ), cPP (39 mmHg vs 37 mmHg,  $p=0.035$ ) compared to the control group. At the same time, no difference in pSBP (127 mmHg vs 123 mmHg,  $p=0.131$ ) and pPP (48 mmHg vs 47 mmHg,  $p=0.365$ ) or HR (58 vs 61 bpm,  $p=0.076$ ) was seen. PPA (1.24 vs 1.30,  $p=0.015$ ) was lower in the AF group than the controls (Table 1).

Multiple linear regression analysis with cfPWV as a dependent variable (adjusted  $R^2=0.37$ ) was performed, where HR, weight, central MAP, eGFR, and group status were considered as predictors. This analysis indicated that AF patients had significantly increased cfPWV ( $\beta=0.500$ ,  $p=0.010$ ) (Table 2).

**Table 2.** Multivariate linear regression analysis (adjusted  $R^2=0.37$ ) using carotid-femoral pulse wave velocity as the dependent variable (n=148)

Variables	Beta	SE of beta	p-value
Sex: female	0.007	0.006	0.291
Age	0.070	0.009	<0.001
Weight	-0.227	0.202	0.263
cMAP	0.019	0.009	0.040
Heart rate	-0.006	0.011	0.552
eGFR	0.019	0.007	0.008
Group: AF	0.500	0.193	0.010

SE – standard error; AF – atrial fibrillation; cMAP – central mean arterial pressure; eGFR – estimated glomerular filtration rate

PPA was significantly lower in patients using BBs compared to patients who did not (1.25 vs 1.30,  $p=0.037$ ). In a multiple linear regression analysis with PPA as a dependent variable (adjusted  $R^2=0.30$ ), where BMI, diagnosis of HT, use of ACEIs or ARBs, and use of BBs were considered as independent variables, the use of BBs was associated with significantly lower PPA ( $\beta=-0.059$ ,  $p=0.017$ ). At the same time, ACEI/ARB use did not have a significant effect on PPA ( $\beta=0.044$ ,  $p=0.243$ ) (Table 3).

**Table 3.** Multivariate linear regression analysis (adjusted R<sup>2</sup>= 0.30) using pulse pressure amplification as the dependent variable (n=150).

Effect	Beta	SE of beta	p-value
Age	-0.007	0.001	<0.001
Sex: female	-0.067	0.021	0.002
BMI	-0.004	0.002	0.087
Diagnosis of hypertension: yes	0.015	0.037	0.677
Use of ACEIs/ARBs: yes	0.044	0.037	0.243
Use of BB: yes	-0.059	0.024	0.017

SE – standard error; BMI – body mass index; ACEIs – angiotensin-converting enzyme inhibitors; ARBs – angiotensin II receptor blockers; BB – beta blockers

### 5.1.3. Comparison of echocardiographic parameters

Patients with AF had mild dilatation of the LA compared to the controls (36.4 ml/m<sup>2</sup> vs 23.1 ml/m<sup>2</sup> vs, p<0.001). Analyzing the AF patients and controls together revealed a positive correlation between LA diameter (r=0.38, p<0.001) and indexed LA volume (r=0.33, p=0.001) with cfPWV. No statistically significant correlations were observed when the subjects of the AF group and the controls were analyzed separately.

A positive correlation of LA diameter with pSBP (r=0.56, p=0.002), cSBP (r=0.51, p=0.005), pPP (r=0.42, p=0.024), and cPP (r=0.38, p=0.043) was also seen in the control group but not in the AF group. The echocardiographic data is presented in Table 4.

**Table 4.** Echocardiographic measurements of patients with atrial fibrillation and control group.

Variable	AF group (n=76)	Control group (n=29)	p-value
Patients with atrial fibrillation during echocardiography, n (%)	28 (37)	0 (0)	<0.001
Ejection fraction, %	58.4 (±9.3)	65.5 (±5.1)	0.001
Interventricular diastolic septum thickness, cm	1.0 (±0.2)	0.8 (±0.1)	<0.001
Left ventricular internal diastolic diameter, cm	4.9 (±0.5)	4.9 (±0.6)	0.368
Posterior wall diastolic thickness, cm	1.0 (±0.2)	0.8 (±0.1)	0.008
Left atrial diameter, cm	4.0 (±0.4)	3.5 (±0.4)	<0.001
Left atrial end systolic volume, ml	74.2 (±22.9)	44.4 (±13.0)	<0.001
Left atrial end systolic volume index, ml/m <sup>2</sup>	36.4 (±9.6)	23.1 (±5.1)	<0.001
Tricuspid annular plane systolic excursion, cm	2.1 (±0.4)	2,2 (±0.3)	0.303
Body surface area, m <sup>2</sup>	2.0 (±0.2)	1.9 (±0.3)	0.007

Values are presented as mean ± SD or count (%); SD – standard deviation; AF – atrial fibrillation

## 5.2. Association of atrial fibrillation with markers of inflammation, oxidative stress, and fibrosis (Paper II)

### 5.2.1. Characteristics of the study population

The baseline characteristics of the study groups is presented in Table 5. There was no age, sex, or height difference between the groups. AF patients were heavier ( $p=0.001$ ) and had a higher BMI ( $p<0.001$ ). No difference in HR or BP was seen.

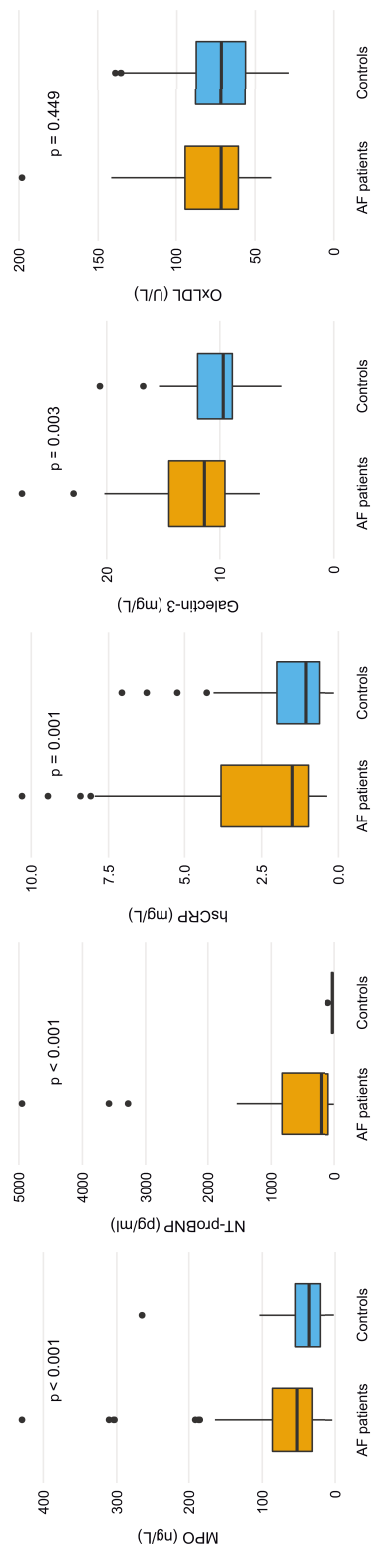
### 5.2.2. Comparison of markers of inflammation, fibrosis, and oxidative stress

Compared to controls, individuals in the AF group had significantly higher levels of NT-proBNP (209.0 vs 28.0 pg/ml,  $p<0.001$ ), Gal-3 (11.4 vs 9.7 mg/L,  $p=0.007$ ), MPO (52.5 vs 36.2 ng/L,  $p<0.001$ ), and hsCRP (1.5 vs 1.1 mg/L,  $p=0.001$ ) without differences in oxLDL (71.5 vs 71.7 U/L,  $p=1$ ) levels between the patients with AF and the controls (Table 5, Figure 1).

**Table 5.** Demographic and clinical characteristics of AF patients and controls.

Variable	AF patients (n=75)	Controls (n=75)	p-value
Age, years	58 ( $\pm 9$ )	57 ( $\pm 11$ )	0.545
Male, n (%)	54 (72)	54 (72)	1.000
Height, cm	175 ( $\pm 10$ )	175 ( $\pm 10$ )	0.949
Weight, kg	90.1 ( $\pm 16.6$ )	81.3 ( $\pm 16.4$ )	0.001
Body mass index, kg/m <sup>2</sup>	29.4 ( $\pm 4.7$ )	26.4 ( $\pm 3.7$ )	<0.001
Heart rate, beats per minute	58 ( $\pm 9$ )	61 ( $\pm 8$ )	0.077
Peripheral systolic blood pressure, mmHg	127 ( $\pm 13$ )	128 ( $\pm 15$ )	0.557
Peripheral diastolic blood pressure, mmHg	78 ( $\pm 9$ )	78 ( $\pm 8$ )	0.861
Peripheral pulse pressure, mmHg	48 ( $\pm 9$ )	50 ( $\pm 11$ )	0.375
hsCRP, mg/L	1.5 (0.9–3.8)	1.1 (0.6–2.0)	0.001
MPO, ng/L	52.6 (31.9–86.0)	36.2 (20.9–54.9)	<0.001
Galectin-3, mg/L	11.4 (9.6–14.5)	9.7 (8.9–12.0)	0.003
OxLDL, U/L	71.5 (60.5–94.3)	71.7 (56.3–87.7)	0.449
NT-proBNP, pg/ml	209.0 (99.5–827.0)	28.0 (20.0–43.0)	<0.001
Ejection fraction, %	58 ( $\pm 9$ )	64 ( $\pm 6$ )	0.015
Left atrial diameter, cm	4.0 ( $\pm 0.5$ )	3.6 ( $\pm 0.4$ )	0.001
Left atrial end systolic volume index, ml/m <sup>2</sup>	36.3 ( $\pm 9.7$ )	23.3 ( $\pm 4.5$ )	<0.001

Values are presented as mean  $\pm$  SD or median (Q1-Q3) or count (%); SD – standard deviation; Q1, Q3 – lower and upper quartile; AF – atrial fibrillation; hsCRP – high-sensitivity C-reactive protein; MPO – myeloperoxidase; OxLDL – oxidized low-density lipoprotein; NT-proBNP – N-terminal pro-brain natriuretic peptide



**Figure 1.** Difference in markers of inflammation and fibrosis between AF patients and controls. The lower and upper limits of the box plots are percentiles; internal horizontal lines indicate medians; vertical lines represent maximal and minimal values; and the circles indicate outliers.

Multivariable logistic regression analysis was performed combining data from the AF patients and the controls to find variables that predicted belonging in the AF patients' group. This analysis indicated that MPO (OR=1.012, p=0.014), hsCRP (OR=1.265, p=0.026), and weight (OR=1.029, p=0.005) were independently associated with the diagnosis of AF, meaning that individuals with higher MPO, hsCRP and weight were more likely to belong to the AF patients' group than in the control group (Table 6).

**Table 6.** Multivariable logistic regression analysis for the association with atrial fibrillation group compared to the control group.

<b>Variables</b>	<b>OR (95% CI)</b>	<b>SE</b>	<b>p-value</b>
<b>MPO</b>	1.012 (1.004–1.024)	0.005	0.014
<b>hsCRP</b>	1.265 (1.041–1.579)	0.105	0.026
<b>Weight</b>	1.029 (1.006–1.053)	0.011	0.013

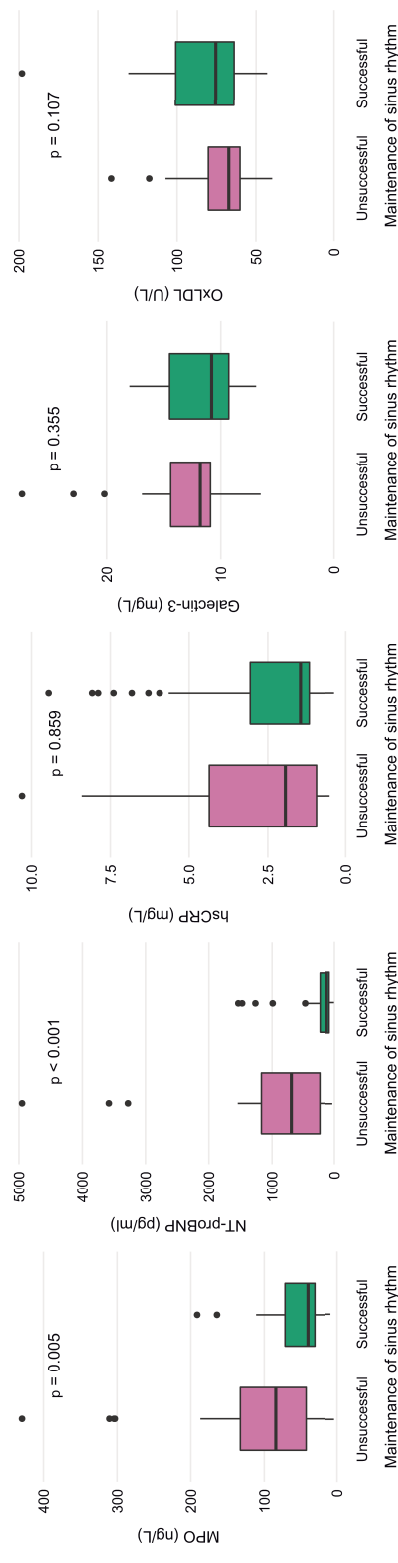
OR – odds ratio; CI – confidence interval; SE – standard error of logarithm of odds ratio; MPO – myeloperoxidase; hsCRP – high-sensitivity C-reactive protein

### 5.2.3. Prognostic importance of biomarkers in the recurrence of atrial fibrillation

Throughout the follow-up period of the study group, 30 patients experienced a recurrence of AF. A comparison was made between the SR subgroup and those who experienced AF episodes during the one-year follow-up period. It was found that the SR subgroup had lower baseline MPO levels compared to those who experienced recurrent AF episodes (40.5 vs 84.3 ng/ml, p=0.005). Additionally, the SR subgroup exhibited lower NT-proBNP values (127.5 vs 694.0 pg/ml, p<0.001). However, no statistically significant differences were detected in hsCRP (1.5 vs 1.9 mg/L, p=0.859), Gal-3 (10.8 vs 11.8 mg/L, p=0.355), or oxLDL (75.7 vs 67.2 U/L, p=0.107) (Figure 2).

Table 7 displays the characteristics of patients who achieved successful and unsuccessful maintenance of SR. It also presents a comparison between patients who maintained SR successfully and the control group. However, two patients in the control group developed AF during the follow-up period and were excluded from the comparison analysis.

Table 8 compares the characteristics of patients who underwent electrical cardioversion or PVI. Both groups had similar age, sex distribution, and height. However, patients in the electrical cardioversion group had a higher body weight. No differences were observed in hemodynamic parameters. The cardioversion group exhibited higher levels of MPO (84.3 vs 40.5 ng/L, p=0.007) and NT-proBNP (991.0 vs 115.5 pg/ml, p<0.001). Additionally, there were more patients with persistent AF (74.1% vs 20.8%, p<0.001) and a recurrence of AF (77.8% vs 18.8%, p<0.001) in the cardioversion group. No differences were noted in LA parameters or the use of antiarrhythmic drugs.



**Figure 2.** Difference in markers of inflammation, fibrosis, and oxidative stress between patients with successful and unsuccessful maintenance of SR during one-year follow-up. The lower and upper limits of the box plots are percentiles; internal horizontal lines indicate medians; vertical lines represent maximal and minimal values; and the circles indicate outliers.

**Table 7.** Characteristics of atrial fibrillation patients comparing maintenance of sinus rhythm after a follow-up of one year and control group.

Variable	Unsuccessful AF patients (n=30)	Successful AF patients (n=45)	Controls (n=73)	p-value (unsuccessful vs successful)	p-value (successful vs controls)
Age, years	59 (±10)	57 (±9)	57 (±11)	0.536	0.739
Male (%)	24 (80.0)	30 (66.3)	52 (71.2)	0.319	0.751
Height, cm	175 (±11)	175 (±10)	175 (±10)	0.911	0.846
Weight, kg	94.0 (±20.0)	87.6 (±13.6)	80.7 (±16.1)	0.102	0.018
Body mass index, kg/m <sup>2</sup>	30.7 (±5.7)	28.6 (±3.6)	26.3 (±3.7)	0.055	0.001
Heart rate, beats per minute	63 (±10)	56 (±8)	61 (±8)	0.002	0.001
Peripheral systolic blood pressure, mmHg	124 (±14)	128 (±12)	128 (±16)	0.168	0.945
Peripheral diastolic blood pressure, mmHg	78 (±8)	78 (±9)	78 (±8)	0.961	0.817
Peripheral pulse pressure, mmHg	46 (±8)	50 (±9)	50 (±11)	0.036	0.985
hsCRP, mg/L	1.9 (1.0–4.4)	1.5 (1.2–3.1)	1.1 (0.6–2.0)	0.859	0.004
MPO, ng/L	84.3 (42.9–132.5)	40.5 (31.0–71.7)	35.1 (20.8–55.4)	0.005	0.052
Galectin-3, mg/L	11.8 (10.9–14.4)	10.8 (9.3–14.5)	9.7 (8.9–12.0)	0.355	0.024
OxLDL, U/L	67.2 (60.1–80.2)	75.7 (64.0–101.1)	71.7 (57.0–87.0)	0.107	0.165
NT-proBNP, pg/ml	694.0 (241.0–1170.0)	127.5 (83.8–237.0)	28.0 (20.0–43.0)	<0.001	<0.001
Ejection fraction, %	54 (±10)	61 (±8)	64 (±6)	<0.001	0.154
Left atrial diameter, cm	4.0 (±0.5)	4.0 (±0.5)	3.6 (±0.4)	0.983	0.002
Left atrial end systolic volume index, ml/m <sup>2</sup>	36.0 (±11.5)	36.6 (±8.4)	23.3 (±4.5)	0.797	<0.001

Values are presented as mean ± SD or median (IQR) or count (%); SD – standard deviation  
 IQR – interquartile range; AF – atrial fibrillation; hsCRP – high-sensitivity C-reactive protein; MPO – myeloperoxidase; OxLDL – oxidized low-density lipoprotein; NT-proBNP – N-terminal pro-brain natriuretic peptide

**Table 8.** Characteristics of atrial fibrillation patients who underwent electrical cardioversion or pulmonary vein isolation.

Variable	Electrical cardioversion (n=27)	Pulmonary vein isolation (n=48)	p-value
Age, years	59 (±10)	57 (±9)	0.370
Male, n (%)	20 (74.1)	34 (70.8)	0.974
Height, cm	175 (±11)	175 (±10)	0.885
Weight, kg	97.1 (±19.2)	86.2 (±13.6)	0.006
Body mass index, kg/m <sup>2</sup>	31.8 (±6.0)	28.1 (±3.2)	<0.001
Heart rate, beats per minute	63 (±10)	56 (±8)	0.002
Peripheral systolic blood pressure, mmHg	124 (±15)	128 (±12)	0.271
Peripheral diastolic blood pressure, mmHg	78 (±9)	79 (±9)	0.765
Peripheral pulse pressure, mmHg	46 (±9)	50 (±9)	0.154
hsCRP, mg/L	2.3 (1.2–4.1)	1.5 (0.9–3.2)	0.223
MPO, ng/L	84.3 (49.8–131.8)	40.5 (30.9–72.1)	0.007
Galectin-3, mg/L	11.4 (10.2–14.8)	11.1 (9.4–14.4)	0.613
OxLDL, U/L	71.4 (61.9–89.2)	73.0 (59.6–94.2)	0.762
NT-proBNP, pg/ml	991.0 (365.0–1240.0)	115.5 (81.0–231.0)	<0.001
Ejection fraction, %	53 (±10)	61 (±7)	<0.001
Left atrial diameter, cm	4.1 (±0.5)	4.0 (±0.5)	0.656
Left atrial end systolic volume index, ml/m <sup>2</sup>	36.0 (±12.0)	36.5 (±8.3)	0.830
CHA <sub>2</sub> DS <sub>2</sub> -VASc score, n (SD)	1.8 (±1.2)	1.3 (±1.2)	0.070
AF type:			
Paroxysmal, n (%)	7 (25.9)	38 (79.2)	<0.001
Persistent, n (%)	20 (74.1)	10 (20.8)	<0.001
Anti-arrhythmic drug:			
None, n (%)	5 (18.5)	5 (10.4)	0.524
Propafenone, n (%)	17 (63.0)	27 (56.3)	0.747
Amiodarone, n (%)	5 (18.5)	8 (16.7)	0.909
Flecainide, n (%)	0 (0)	8 (16.7)	NA
Use of beta-blockers, n (%)	22 (81.5)	45 (93.8)	0.207
AF recurrence during 1-year follow-up, n (%)	21 (77.8)	9 (18.8)	<0.001

Values are presented as mean ± SD or median (IQR) or count (%); SD – standard deviation  
IQR – interquartile range; hsCRP – high-sensitivity C-reactive protein; MPO – myeloperoxidase;  
OxLDL – oxidized low-density lipoprotein; NT-proBNP – N-terminal pro-brain natriuretic peptide

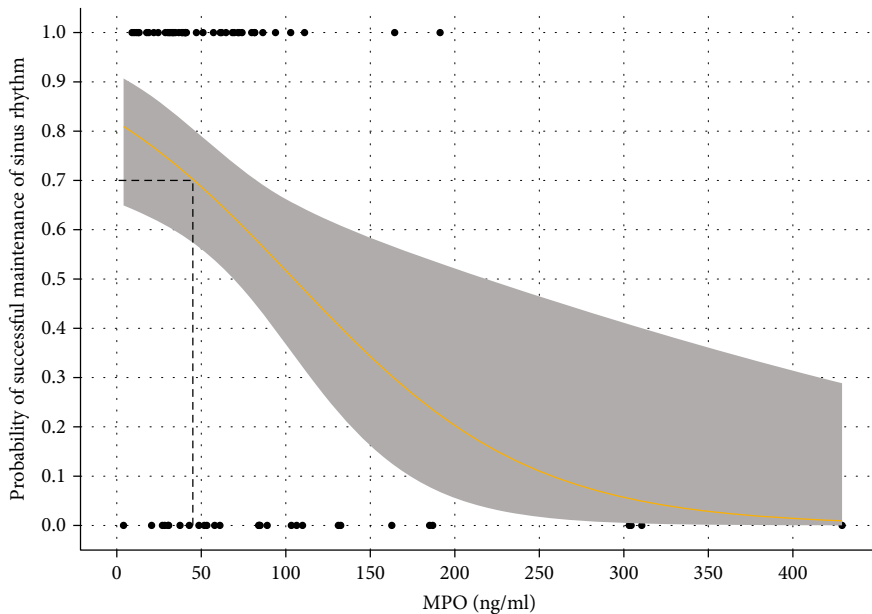
In the study population, a multivariable logistic regression analysis was conducted with AF recurrence as the dependent variable. When LA diameter, age, and AF type were included in the analysis (Table 9), MPO (OR=0.985, p=0.010) was found to be independently associated with AF recurrence. BMI, PP, pSBP, pDBP did not exhibit any association with repeated episodes of AF (data not shown).

**Table 9.** Multivariable logistic regression analysis for recurrence of atrial fibrillation.

Variables	OR (95% CI)	SE	p-value
Age	1.014 (0.930–1.109)	0.044	0.757
Left atrial diameter	0.767 (0.156–3.794)	0.798	0.740
AF type: persistent	0.016 (0.002–0.074)	0.886	<0.001
MPO	0.985 (0.970–0.994)	0.006	0.010

OR – odds ratio; CI – confidence interval; SE – standard error of logarithm of odds ratio; MPO – myeloperoxidase; AF type – paroxysmal or persistent atrial fibrillation

Figure 3 displays the interpreted predicted probabilities computed for MPO. For instance, patients who had a baseline MPO level lower than 46 ng/ml had a probability of at least 70% maintaining SR after a one-year follow-up period, irrespective of the intervention selected.



**Figure 3.** Probability of successful maintenance of SR compared to MPO levels. The circles represent the MPO values of patients with successful maintenance of SR or atrial fibrillation recurrence. The yellow line represents the probability of SR maintenance associated with different MPO values, and the grey area represents upper and lower confidence intervals. The dotted lines indicate a cut-off value of 46 ng/ml where probability of SR maintenance is 70% during the follow-up period of one year. MPO – myeloperoxidase; SR – sinus rhythm

### **5.3. Oral anticoagulation use of ≥65-year-old atrial fibrillation patients in Estonia and its relationship with relative survival (Paper III)**

#### **5.3.1. Comparison of the study cohorts**

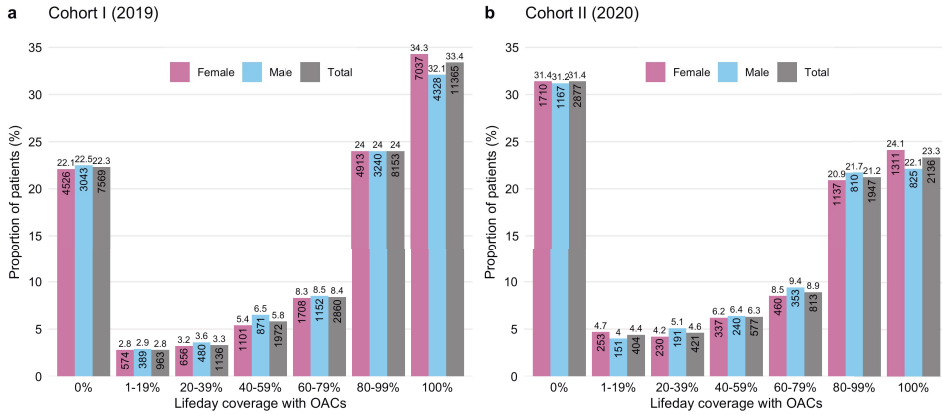
Cohort I included 34,018 patients (60.3% females) with a mean age of 78.1 (SD=7.3) years, while cohort II had 9,175 patients with a new AF documentation (59.3% females) with a mean age of 77.5 (SD=8.2) years. In cohorts I and II, 26,449 (77.7%) and 6,298 (68.6%) patients, respectively, had at least one prescription of OAC. Cohort II patients exhibited a younger age (77.5 vs 78.2 years,  $p<0.001$ ) and a greater occurrence of comorbidities such as cancer (14.8% vs 13.9%,  $p=0.024$ ), renal insufficiency (11.5% vs 9.7%,  $p<0.001$ ), CAD (13.4% vs 12.3%,  $p=0.003$ ), and coronary stenting (8.2% vs 7.0%,  $p<0.001$ ). Conversely, cohort I patients had a higher prevalence of diabetes (23.4% vs 22.3%,  $p=0.021$ ) and HT (88.4% vs 86.7%,  $p<0.001$ ). The baseline characteristics of the study cohorts are presented in Table 10.

**Table 10.** Baseline characteristic of cohorts I and II

<b>Variable</b>	<b>Cohort I (2019)</b>	<b>Cohort II (2020)</b>	<b>p-value</b>
<b>Total patients, n</b>	3,4018	9175	
<b>Mean age, years (SD)</b>	78.1 (7.3)	77.5 (8.2)	<0.001
<b>Age 65–74, n (%)</b>	11,197 (32.9)	3,551 (38.7)	<0.001
<b>≥75, n (%)</b>	22,821 (67.1)	5,624 (61.3)	
<b>Female, n (%)</b>	20,515 (60.3)	5,438 (59.3)	0.074
<b>Cancer, n (%)</b>	4,733 (13.9)	1,362 (14.8)	0.024
<b>Diabetes, n (%)</b>	7,968 (23.4)	2,043 (22.3)	0.021
<b>Hypertension, n (%)</b>	30,059 (88.4)	7,953 (86.7)	<0.001
<b>CAD, n (%)</b>	4,180 (12.3)	1,234 (13.4)	0.003
<b>Stroke, n (%)</b>	3,962 (11.6)	1,136 (12.4)	0.055
<b>PAD, n (%)</b>	1,764 (5.2)	501 (5.5)	0.307
<b>Renal insufficiency, n (%)</b>	3,313 (9.7)	1,051 (11.5)	<0.001
<b>Coronary stent, n %</b>	2,375 (7.0)	756 (8.2)	<0.001
<b>Use of ≥1 OACs, n (%)</b>			
<b>1</b>	21,412 (76.2)	6,327 (89.6)	<0.001
<b>2</b>	6,221 (22.1)	686 (9.7)	<0.001
<b>3</b>	445 (1.6)	49 (0.7)	<0.001
<b>4</b>	14 (0.0)	3 (0.0)	<0.001
<b>OAC monotherapy, n (%)</b>			
– warfarin	2,950 (13.8)	134 (2.1)	<0.001
– dabigatran	2,702 (12.6)	763 (12.1)	0.246
– rivaroxaban	8,261 (38.6)	2,311 (36.5)	0.003
– abixaban	7,499 (35.0)	3,092 (48.9)	<0.001
– edoxaban	0 (0)	27 (0.4)	NA
<b>OAC lifieday coverage</b>			
<b>0%</b>	7,569 (22.2)	2,877 (31.4)	<0.001
<b>1–79%</b>	6,931 (20.4)	2,215 (24.1)	
<b>≥80%</b>	19,518 (57.4)	4,083 (44.5)	

OAC – oral anticoagulant; CAD – coronary artery disease; PAD – peripheral artery disease

In cohort I, 57.4% of patients (55.6% of men and 57.7% of women) had an LDC of prescribed OACs  $\geq 80\%$ , while in cohort II this percentage was 44.5% (43.8% of men and 45.0% of women). The LDC distribution was U-shaped in both cohorts, with the majority of patients concentrated at the extremes of the spectrum. Figure 4 displays the distribution of LDC.



**Figure 4.** Lifeday coverage of oral anticoagulant prescriptions for cohorts I and II. The number of males, females, and total patients in different lifeday coverage groups is shown with the proportion of patients in percentages. OAC – oral anticoagulant

We categorized both cohorts into three groups based on LDC proportions: 0%, 1–79%, and  $\geq 80\%$ . Patients in the LDC 0% group of cohort I had a higher prevalence of stroke compared to the groups where OACs were prescribed. At the same time, a lower prevalence of diabetes and HT was observed in the LDC 0% groups. Contrary to cohort I, there were more patients with HT in the LDC  $\geq 80\%$  group in cohort II compared to the 0% group.

In cohort I, out of 34,018 patients, 19,518 (57.4%) had a LDC of  $\geq 80\%$ . Among them, 14,448 patients (74%) were prescribed one OAC, and 4,733 patients (24.2%) were prescribed two different OACs during the one-year follow-up period. Only a small percentage of patients were prescribed three (1.7%) or four (0.1%) different OACs during the study period.

In cohort II, out of 9,175 patients, 4,083 (44.5%) had a LDC of  $\geq 80\%$ . Among them, 6,327 (89.6%) were prescribed one OAC, and 686 patients (9.7%) were prescribed two different OACs. Three or four different OACs were prescribed in 0.7% and 0.0% of the cases, respectively.

Tables 11 and 12 present the characteristics of the different LDC groups, including age, sex, concomitant disease, and different OAC use.

**Table 11.** Comparison of different oral anticoagulant lifeday coverage groups related to age, sex, and concomitant disease in cohort I.

Variable	Cohort I (2019)				p-values for the differences between OAC lifeday coverage groups		
	0%	1–79%	≥80%	0% vs 1–79%	0% vs ≥80%	1–79% vs ≥80%	
<b>OAC lifeday coverage</b>							
Patients, n (%)	7,569 (22.3)	6,931 (20.3)	19,518 (57.4)				
Mean age, y (SD)	78.9 (7.9)	78.1 (7.1)	77.9 (7.0)	<0.001	<0.001	0.149	
Age 65–74, n (%)	2,384 (31.5)	2,302 (33.2)	6,511 (33.4)	0.057	0.011	0.836	
≥75, n (%)	5,185 (68.5)	4,629 (66.8)	13,007 (66.6)				
Female, n (%)	4,526 (59.8)	4,039 (58.3)	11,950 (61.2)	0.065	0.063	<0.001	
Cancer, n (%)	1,165 (15.4)	976 (14.1)	2,592 (13.3)	0.056	<0.001	0.097	
Diabetes, n (%)	1,560 (20.6)	1,622 (23.4)	4,786 (24.5)	<0.001	<0.001	0.064	
Hypertension, n (%)	6,423 (84.9)	6,153 (88.8)	17,483 (89.6)	<0.001	<0.001	0.067	
CAD, n (%)	959 (12.7)	913 (13.2)	2,308 (11.8)	0.380	0.120	0.010	
Stroke, n (%)	1,025 (13.5)	743 (10.7)	2,194 (11.2)	<0.001	<0.001	0.240	
PAD, n (%)	431 (5.7)	374 (5.4)	959 (4.9)	0.455	0.029	0.244	
Renal insufficiency, n (%)	818 (10.8)	697 (10.1)	1,798 (9.2)	0.147	<0.001	0.082	
Coronary stent, n %	486 (6.4)	515 (7.4)	1,374 (7.0)	0.054	0.150	0.290	
<b>Use of ≥1 OACs, n (%)</b>							
– 1	0 (0.0)	5,420 (78.2)	14,448 (74.0)			<0.001	
– 2	0 (0.0)	1,394 (20.1)	4,733 (24.2)			<0.001	
– 3	0 (0.0)	115 (1.7)	325 (1.7)			1.000	
– 4	0 (0.0)	2 (0.0)	12 (0.1)			0.480	
<b>OAC monotherapy, n (%)</b>							
– warfarin	0 (0.0)	514 (9.5)	2,302 (15.9)			<0.001	
– dabigatran	0 (0.0)	728 (13.4)	1,715 (11.9)			<0.001	
– rivaroxaban	0 (0.0)	1,820 (33.6)	5,863 (40.6)			<0.001	
– abixaban	0 (0.0)	2,358 (43.5)	4,568 (31.6)			<0.001	
– edoxaban	0 (0.0)	0 (0.0)	0 (0.0)			1.000	

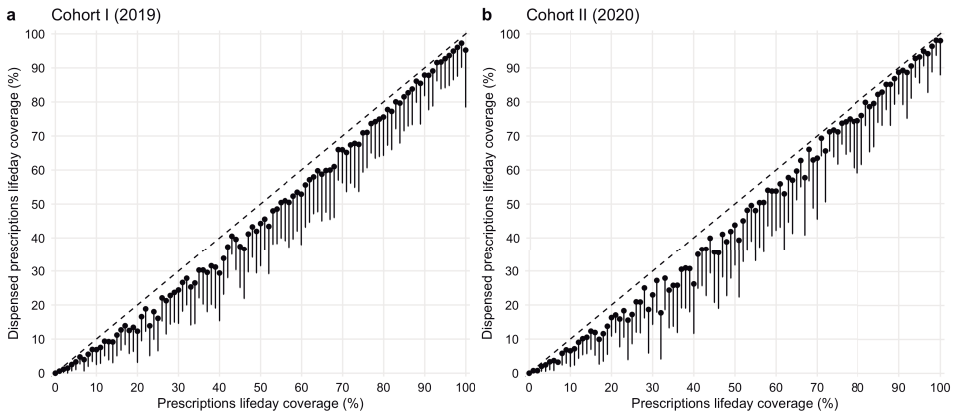
OAC – oral anticoagulant; CAD – coronary artery disease; PAD – peripheral artery disease; SD – standard deviation

**Table 12.** Comparison of different oral anticoagulant lifeday coverage groups related to age, sex, and concomitant disease in cohort II.

Variable	Cohort II (2020)				p-values for the differences between OAC lifeday coverage groups	
	0%	1–79%	≥80%	0% vs 1–79%	0% vs ≥80%	1–79% vs ≥80%
<b>OAC lifeday coverage</b>						
Patients, n (%)	2,877 (31.4)	2,215 (24.1)	4,083 (44.5)			
Mean age, y (SD)	78.4 (8.5)	77.2 (8.1)	77.0 (8.1)	<0.001	<0.001	0.610
Age 65–74, n (%)	1,037 (36.0)	866 (39.1)	1,648 (40.4)	0.083	0.001	1
≥75, n (%)	1,840 (64.0)	1,349 (60.9)	2,435 (59.6)			
Female, n (%)	1,710 (59.4)	1,280 (57.8)	2,448 (60.0)	0.743	1	0.300
Cancer, n (%)	451 (15.7)	311 (14.0)	600 (14.7)	0.341	0.825	1
Diabetes, n (%)	620 (21.6)	458 (20.7)	965 (23.6)	1	0.132	0.024
Hypertension, n (%)	2,416 (84.0)	1,919 (86.6)	3,618 (88.6)	0.028	<0.001	0.072
CAD, n (%)	396 (13.8)	277 (12.5)	561 (13.7)	0.609	1	0.542
Stroke, n (%)	352 (12.2)	217 (9.8)	567 (13.9)	0.021	0.147	<0.001
PAD, n (%)	164 (5.7)	115 (5.2)	222 (5.4)	1	1	1
Renal insufficiency, n (%)	352 (12.2)	259 (11.7)	440 (10.8)	1	0.194	0.862
Coronary stent, n (%)	222 (7.7)	178 (8.0)	356 (8.7)	1	0.442	1
<b>Use of ≥1 OACs, n (%)</b>						
– 1	0 (0.0)	1,922 (86.8)	3,663 (89.7)			<0.001
– 2	0 (0.0)	272 (12.3)	392 (9.6)			0.001
– 3	0 (0.0)	19 (0.9)	27 (0.7)			0.472
– 4	0 (0.0)	2 (0.1)	1 (0.0)			NA
<b>OAC monotherapy, n (%)</b>						
– warfarin	0 (0.0)	33 (1.7)	92 (2.5)			0.048
– dabigatran	0 (0.0)	216 (11.2)	427 (11.7)			0.401
– rivaroxaban	0 (0.0)	629 (32.7)	1403 (38.3)			<0.001
– abixaban	0 (0.0)	1019 (53.0)	1739 (47.5)			0.010
– edoxaban	0 (0.0)	25 (1.3)	2 (0.1)			NA

OAC – oral anticoagulant; CAD – coronary artery disease; PAD – peripheral artery disease; SD – standard deviation

In both cohorts, we observed a clear correlation (Pearson’s correlation coefficients of 0.96 and 0.98 for cohorts I and II, respectively) between the LDC of prescribed OACs and the LDC of dispensed prescriptions, as illustrated in Figure 5.



**Figure 5.** Differences between the LDC of prescribed OACs and dispensed prescriptions for cohorts I and II for cohorts I and II. Patients are grouped by prescribed lifieday coverage in 1% increments. The diagonal line represents the LDC of prescribed OACs in percentages. Dots represent the proportion of dispensed prescriptions with a lower 95% confidence interval.

During the one-year follow-up period, 3,042 patients (9.0%; 1,279 men and 1,762 women) and 961 patients (10.5%; 411 men and 550 women) died in cohort I (2019) and cohort II (2020), respectively. The observed survival rates at one year for the LDC groups 0%, 1–79%, and  $\geq 80\%$  were 85.3% (95% CI 84.5–86.1%), 92.3% (95% CI 91.7–93.0%), and 92.6% (95% CI 92.5–93.2%), respectively, for cohort I and 85.9% (95% CI 84.6–87.2%), 89.8% (95% CI 88.5–91.0%), and 92.0 (95% CI 91.2–92.9%), respectively, for cohort II. The all-cause mortality rate for the Estonian population aged  $\geq 65$  years was 4.7% for both years.

In both cohorts, the observed and relative survival rates were significantly lower in the LDC 0% group compared to the other LDC groups (all p-values  $< 0.001$ ). However, the survival of patients with LDC 1–79% and  $\geq 80\%$  did not differ significantly in cohort I, while patients in the  $\geq 80\%$  group showed better survival than those in the 1–79% group in cohort II. The relative survival of male patients was similar to that of female patients, but younger patients (aged 65–74 years) tended to have increased relative survival compared to older patients (aged  $\geq 75$  years), as shown in Tables 13 and 14. Figure 6 compares the relative survival curves of different LDC groups compared to the expected all-cause survival of the general age-matched population from the same years.

**Table 13.** The observed and relative survival estimates at one year for LDC groups in cohort I.

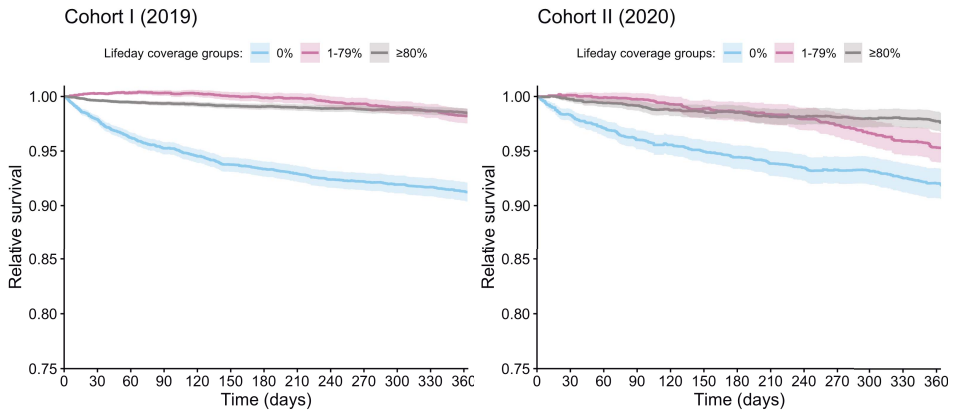
	<b>Patients</b>	<b>Observed mean survival % (95% CI)</b>	<b>p-values for observed survival curve differences*</b>	<b>Expected mean survival (%)</b>	<b>Relative survival % (95% CI)</b>	<b>p-value for net survival curve differences*</b>
<b>LDC groups</b>						
<b>0%</b>	7,569	85.3 (84.5–86.1)	–	95.3	91.2 (90.4–92.1)	–
<b>1–79%</b>	6,931	92.3 (91.7–93.0)	<0.001	95.3	98.2 (97.6–98.9)	<0.001
<b>≥80%</b>	19,518	92.9 (92.5–93.2)	<0.001	95.3	98.5 (98.1–98.9)	<0.001
<b>Age groups</b>						
<b>65–74</b>	11,197	95.3 (94.9–95.7)	–	97.8	97.8 (97.4–98.2)	–
<b>≥75</b>	22,821	89.0 (88.6–89.4)	<0.001	92.6	96.3 (95.9–96.8)	<0.001
<b>Sex</b>						
<b>Female</b>	20,515	91.4 (91.0–91.8)	–	97.2	96.7 (96.3–97.2)	–
<b>Male</b>	13,503	90.5 (90.0–91.0)	0.006	98.1	96.9 (96.4–97.4)	0.629

\* p-values are not adjusted for multiple testing; LDC – lifestay coverage; CI – confidence interval

**Table 14.** The observed and relative survival estimates at one year for LDC groups in cohort II.

	<b>Patients</b>	<b>Observed mean survival % (95% CI)</b>	<b>p-values for observed survival curve differences*</b>	<b>Expected mean survival (%)</b>	<b>Relative survival % (95% CI)</b>	<b>p-values for net survival curve differences*</b>
<b>LDC groups</b>						
<b>0%</b>	2,877	85.9 (84.6–87.2)	–	95.3	91.9 (90.5–93.3)	–
<b>1–79%</b>	2,215	89.8 (88.5–91.0)	<0.001	95.3	95.2 (93.9–96.6)	<0.001
<b>≥80%</b>	4,083	92.0 (91.2–92.9)	<0.001	95.3	97.6 (96.7–98.5)	<0.001
<b>Age groups</b>						
<b>65–74</b>	3,551	94.3 (93.6–95.1)	–	97.8	96.6 (95.8–97.4)	–
<b>≥75</b>	5,624	86.5 (85.7–87.4)	<0.001	92.4	94.3 (93.4–95.3)	<0.001
<b>Sex</b>						
<b>Female</b>	5,438	89.9 (89.1–90.7)	–	95.7	95.4 (94.5–96.1)	–
<b>Male</b>	3,737	89.0 (88.0–90.0)	0.138	94.4	95.0 (93.9–96.1)	0.581

\* p-values are not adjusted for multiple testing; LDC – lifestage coverage; CI – confidence interval



**Figure 6.** Comparison of relative survival curves for  $\geq 65$ -year-old patients in Estonia. Patients with one-year follow-ups were divided into three lifeday coverage groups. Relative survival was calculated as the ratio of the observed all-cause survival of all the patients to the expected all-cause survival in the general population.

## 6. DISCUSSION

### 6.1. Central hemodynamics and arterial stiffness of patients with atrial fibrillation (Paper I)

Paper I found that patients with AF had higher cfPWV, indicating increased AS. Additionally, elevated cSBP and cPP with lower PPA were observed when compared to controls, although no difference in pBP was seen. This seems to indicate a higher residual CV risk of AF patients, even with controlled pBP. The higher cBP seems to be an important factor leading to AS and increased cfPWV causing subclinical organ damage.

Studies on the vasculature have provided valuable information on pressure wave propagation and reflections and their impact on central and peripheral BP. The Strong Heart Study has shown that cBP is a better predictor of CV events in subjects without known CVD than pBP (Roman *et al.* 2007). This is because cBP is more closely related to the loading conditions of the heart, brain, and other organs susceptible to hypertension-mediated organ damage. As a result, reducing cBP using antihypertensive medications has been found to better predict further CV events than pBP (Williams *et al.* 2006).

AS is a well-established indicator of CV risk, and the measurement of cfPWV is widely accepted as the gold standard for assessing AS (Townsend *et al.* 2015). It has been identified as an independent predictor of primary coronary events (Boutouyrie *et al.* 2002) and stroke (Laurent *et al.* 2003) in HT patients. As numerous studies have pointed to the importance of AS in CVDs, more research has focused on its role in AF. There have been some conflicting studies published previously. A prior study with 34 patients and 31 controls found no variation in cfPWV between patients with the first episode of AF and healthy subjects (Kilicgedik *et al.* 2017). However, the mean age of the participants was younger, the prevalence of HT was lower, and the study excluded patients with LA diameter over 40 mm. In comparison, the subjects in our study group were in a more advanced stage of the disease, which may explain the difference in results. Another study by Kizilirmak *et al.* (2015) compared cBP and AS in patients with paroxysmal AF and a control group. They discovered that patients with paroxysmal AF had higher cBP and increased cfPWV, as well as significant differences in pBP, which correlated with differences in cBP. In our study, despite no variation in pBP, the AF group demonstrated higher cSBP and cPP, indicating higher risk of CV adverse events.

Lamante *et al.* (2008) found a correlation between PWV and PP (a surrogate marker for AS) and LA size in hypertensive patients with no prior AF episodes. This correlation was also supported by another study with 111 hypertensive patients (Janwanishstaporn and Boonyasirinant 2016) and a larger prospective observational study that demonstrated pPP's predictive value for AF incidence (Mitchell *et al.* 2007). These findings suggest that AS can lead to atrial enlargement, which is a known risk factor for AF (Vaziri *et al.* 1994; Tsang *et al.* 2001;

Parkash *et al.* 2004). AS affects cardiac remodeling, left ventricular geometry, and diastolic function (Palmieri *et al.* 2003), all of which contribute to the relationship between LA size and AF risk (Cioffi *et al.* 2004). Our study found that AF patients had larger LA diameter, indexed LA end-systolic volume, and increased AS compared to the control group. While we observed a positive correlation between cfPWV and LA size and volume when we analyzed AF patients and controls together, this correlation was not significant in the AF group. The reason for this might be that all AF patients were managed using a rhythm control strategy, which is usually opted for patients with milder structural changes in the heart.

HT is a prevalent, independent, and modifiable risk factor for AF (Healey and Connolly 2003). In our study, 65% had a diagnosis of HT. As both diseases become more prevalent with age, it is common to see these conditions coexisting in patients (Healey and Connolly 2003). The majority of our patients (90%) used BBs for rate, initial rhythm control and BP management, with metoprolol being the most commonly used (90% of all BBs). However, BBs have a smaller effect on cBP than pBP, which may explain why the study group had higher cPP and cSBP values and may also explain the higher cfPWV.

BBs have been criticized for their unfavorable effect on cBP, as shown by a meta-analysis published by Law *et al.* (2009), where a slight inferiority of BBs in preventing stroke was seen. The Conduit Artery Function Evaluation (CAFE) Study (Williams *et al.* 2006) demonstrated that ACEIs, ARBs, and CCBs were more effective at reducing cBP compared to cardioselective BBs like atenolol, a finding that was confirmed by a meta-analysis by Manisty and Hughes (2013). However, our recent study found that nebivolol, a vasodilating BB, was more effective at reducing cBP, cPP, and left ventricular wall thickness than metoprolol, with similar reductions in pBP and HR (Kampus *et al.* 2011). This indicates that not all BBs have an equal effect on central hemodynamics, as was also shown by Dhakam *et al.* (2008), where superior cBP reduction by nebivolol was seen compared to atenolol. It is possible that non-vasodilating BBs may increase cBP through a reduction in HR (Williams *et al.* 2006; Kampus *et al.* 2011), but our study of pacemaker patients did not show any increase in cBP in patients with lower HR (Teeäär *et al.* 2018). Additionally, atenolol's inferior ability to reduce cBP may be related to both heart rate-dependent and -independent mechanisms, as demonstrated by Teeäär *et al.* (2020).

The guidelines for managing AF and HT suggest that BBs should be the first-line drugs for rate or initial rhythm control in AF patients (Kirchhof *et al.* 2016; Hindricks *et al.* 2021). However, our study found that BBs were associated with lower PPA, which is consistent with previously mentioned studies that showed BBs have a smaller effect on cBP compared to other antihypertensive drugs (Williams *et al.* 2006; Manisty and Hughes 2013). These findings emphasize the importance of assessing cBP in managing the higher CV risk in AF patients and suggest that vasodilating BBs or nondihydropyridine CCBs may be a better choice for rate control and BP management in AF patients. Combination therapy of BBs with ACEIs or ARBs may also be beneficial in targeting cBP and reducing the residual

risk associated with higher cBP (Xie *et al.* 2017). Further studies are needed to compare the impact of nondihydropyridine CCBs and vasodilating BBs on central hemodynamics and HR in AF patients.

Although AS may provide a novel target for AF prevention, the optimal pharmacologic therapy for reducing AS has not yet been established. Previous studies with hypertensive patients suggest that ACEIs may have a potential impact on AS, which is partly independent of BP (Mallareddy *et al.* 2006; Xie *et al.* 2017). Two recently published meta-analyses also showed that ACEIs can reduce PWV in comparison to placebo, but not in comparison to other antihypertensive drugs (Shahin *et al.* 2012; Li *et al.* 2020). However, in our study, ACEIs and ARBs did not have any significant effects on PPA or cFPWV (data not shown).

### 6.1.1. Limitations

The study has some limitations that need to be addressed. One unique aspect of our study was that we made all hemodynamic measurements in SR for both groups. This approach was intended to address potential inaccuracies in central hemodynamic measurements caused by HR variability in patients with AF, which could improve measurement accuracy. However, this approach may lead to different results in patients with ongoing AF.

Hemodynamic profiling and AS assessment in patients with AF have been challenging due to the difficulty in accurately measuring central BP and AS non-invasively in these patients. This is due to the inability to validate these methods in patients with frequent extrasystoles and the increased HR variability associated with AF that can disturb or make the measurements impossible (Van Bortel *et al.* 2002). A previous proof of concept study found that cFPWV and cPP measurements were feasible in patients with ongoing AF when compared to measurements taken after cardioversion (Caluwé *et al.* 2018). More validation is needed to confirm this. Therefore, in our study, we only included patients in SR to minimize measurement inaccuracies.

Since our study was cross-sectional, we cannot make strong causal claims. Additionally, we combined patients with paroxysmal and persistent AF and analyzed them as one group. When we examined the groups separately, we found no differences in pBPs, cFPWV, or pPP between them. However, the cardioversion group had a lower cPP (36 mmHg vs 41 mmHg,  $p = 0.020$ ) and HR (63 vs 56 bpm,  $p = 0.002$ ). We combined the groups due to the small sample size to maintain statistical power. It should also be noted that there was a difference in sex, weight, BMI, HDL and eGFR between the groups that could also impact the results of the study.

Regarding PPA, it should be pointed out that all of the patients who used BBs also had AF. This may impact the findings and the role of AF or BBs regarding reduced PPA in the AF group can not be clearly differentiated.

The study population mainly used metoprolol as the BB, but since BBs have different affinities to beta receptors, other drugs in the group could impact central hemodynamics differently.

## 6.2. Markers of inflammation, fibrosis, and oxidative stress in patients with atrial fibrillation (Paper II)

Paper II found that individuals with AF had elevated levels of MPO, NT-proBNP and Gal-3 in comparison to the control group. Additionally, the multivariate analysis revealed that MPO was independently associated with AF. Moreover, the secondary analysis revealed that higher baseline levels of MPO were independently associated with recurring episodes of AF during the one-year follow-up period.

The pathogenesis of AF is intricate and involves an interplay between inflammatory response (Guo *et al.* 2012; Hu *et al.* 2015), OxS (Korantzopoulos *et al.* 2007; Korantzopoulos *et al.* 2018), and development of atrial fibrosis (Dzeshka *et al.* 2015). These processes lead to the electrical and structural remodeling of the atria, which explains the progressive nature of the disease (Dzeshka *et al.* 2015). The role of different biomarkers in predicting the effectiveness of rhythm control therapies is an important focus in AF research. Accumulating evidence suggests that chronic inflammation can modify atrial electrophysiology, increasing susceptibility to AF (Hu *et al.* 2015). Large prospective cohort studies such as the Cardiovascular Health Study (Aviles *et al.* 2003) have demonstrated that CRP is associated with the presence of AF and can also predict new-onset AF. Additionally, data suggests that AF itself can sustain the inflammatory response in the body, contributing to atrial remodeling (Korantzopoulos *et al.* 2018). This creates a vicious cycle that may contribute to the progressive nature of AF. Watanabe *et al.* (2006) found that hsCRP was an independent predictor of successful cardioversion of AF and its recurrence after electrical cardioversion. These results were confirmed in a meta-analysis by Yo and colleagues (Yo *et al.* 2014).

Our study showed significantly higher levels of hsCRP in patients with AF compared to the controls. However, we did not find differences between patients who successfully maintained SR after one year and those who did not. This may be due to the relatively short duration of AF before aggressive rhythm control was initiated and the paroxysmal nature of AF in patients with PVI. Additionally, we excluded patients with HF and other potential confounding factors that might increase hsCRP levels.

Gal-3 is a member of the lectin protein family that participates in cell differentiation, fibrinogenesis, and inflammation (Dong *et al.* 2018). Gal-3 has been shown to activate (myo)fibroblasts and endocardial cells by increasing the ECM, leading to fibrosis (Henderson and Sethi 2009). While Gal-3 is a critical factor in the initial phase of the inflammatory response, inducing neutrophil and mast cell activation, it also plays a role in transitioning to chronic inflammation by causing fibrogenesis and tissue fibrosis (Henderson and Sethi 2009). Studies have shown that Gal-3 is closely associated with AF (Ho *et al.* 2014; Fashanu *et al.* 2017). Our study also found that AF patients had significantly higher levels of Gal-3 than controls, suggesting the presence of low-grade inflammatory and fibrotic processes in AF patients. A recent meta-analysis (Zhang and Wu 2019) indicated that Gal-3 is a predictor of AF ablation outcomes. The findings showed higher Gal-3

levels in patients with recurrent AF after ablation, and this association was independent of age, gender, and LA dimensions. In the studies included in the meta-analysis, Gal-3 ranged from 6.03 to 30.8 ng/ml in the AF recurrence group and 5.7 to 24.5 ng/ml in the group without AF episodes. Compared to the mean values of our study group (13.0 ng/ml with AF recurrence vs 11.7 ng/ml without AF recurrence), the values of Gal-3 were lower in all our AF patients. Furthermore, most studies included a considerable proportion of patients with persistent AF, indicating advanced stages of the disease. In terms of maintaining SR after one year, we did not find a difference in Gal-3 between the AF groups. This might be due to the relatively early stages of the disease in our study group, as evidenced by the low levels of Gal-3 in all of our AF patients, as well as the small sample size.

The diagnostic significance of BNP and its inactive form, NT-proBNP, in HF is well established, but their role in AF remains uncertain. Normally, the hormone is synthesized in response to increased wall stress in the heart caused by increased loading conditions. However, in AF patients, NT-proBNP reflects volume overload in the atria, and its levels are thought to be increased due to the high frequency of atrial contractions and local atrial inflammation (Möllmann *et al.* 2008). NT-proBNP has also been associated with the degree of fibrosis in the atria of patients with AF (Hwang *et al.* 2009) and has been shown to correlate with serum markers of collagen turnover (Ravassa *et al.* 2015). Our study found that AF patients had higher NT-proBNP levels than controls, but the levels were lower in the group that maintained SR during the follow-up period. Additionally, population-based studies suggest that NT-proBNP levels can predict new-onset AF, regardless of other risk factors for AF (Asselbergs *et al.* 2008).

Furthermore, two meta-analyses have demonstrated the predictive role of NT-proBNP in assessing the recurrence rate of AF after ablation (Zhang *et al.* 2016) and electrical cardioversion (Xu and Tang 2017). In our study, NT-proBNP was not independently associated with AF recurrence when age, MPO, AF type, and LA diameter were used as variables. However, higher levels of NT-proBNP were found in the subgroup of patients with a more persistent form of AF. As NT-proBNP is a marker of volume overload in the atria (Möllmann *et al.* 2008) and seems to correlate with disease progression, a strong relationship between persistent AF and NT-proBNP could potentially influence our analysis.

MPO has been implicated in the interplay between inflammation and OxS, which contributes to cardiac fibrosis (Ndrepepa 2019). This enzyme possesses bactericidal properties and is predominantly released by activated polymorphonuclear neutrophils (Friedrichs *et al.* 2012). Upon activation, MPO is secreted into the extracellular environment and undergoes oxidation, leading to the generation of reactive oxygen species by reacting with various molecules (Friedrichs *et al.* 2012). Notably, MPO triggers the production of hypochlorous acids, particularly hypochlorous acid, which activates MMPs and inhibits tissue inhibitors of MMPs (Ndrepepa 2019).

These processes, among others, promote increased ECM turnover, collagen accumulation, and fibrosis in the atrial tissue (Friedrichs *et al.* 2012). Although MPO has been linked to various CVDs (Ndrepepa 2019), its role in AF remains

relatively unclear. A limited number of clinical studies have explored the connection between MPO and AF. For instance, Li *et al.* (2013) found that higher MPO levels may predict arrhythmia recurrence after AF ablation. Similarly, Holoz-wirth *et al.* (2020) reported elevated MPO levels in 23 patients with AF undergoing PVI, but no differences in baseline MPO levels, regardless of the rhythm outcome. The small sample size and the inclusion of a heterogeneous group of AF patients were suggested as potential reasons for this finding. In our study, we found a significant association between MPO and AF in a multivariate analysis, as well as higher recurrence rates of the arrhythmia after electrical cardioversion or ablation (rhythm control). These findings are consistent with those reported by Li *et al.* (2013), and suggest that MPO may serve as a clinically useful prognostic marker for assessing AF recurrence.

The role of non-physiological OxS in the development of AF has gained increasing attention. In addition to inflammation, non-physiological OxS has been found to play a crucial part in atrial remodeling (Korantzopoulos *et al.* 2003). Mihm *et al.* (2001) demonstrated marked elevation of OxS markers in their study of chronic AF patients who underwent the Maze procedure, which was the first of its kind. While several markers of OxS have been linked to AF (Samman Tahhan *et al.* 2017) the role of oxLDL is still not well understood. A small study found higher levels of oxLDL in AF patients without other risk factors and its association with HT (Polovina *et al.* 2015). In our study, we investigated the importance of malondialdehyde-modified low-density lipoprotein (MDA-LDL), a subtype of oxLDL and a well-recognized risk marker for CVD, particularly atherosclerosis (Lopes-Virella and Virella 2019). We found no significant difference in MDA-LDL levels between the study group and controls, nor between patients with sustained SR and those with recurring AF. Another study on patients with AF undergoing PVI ablation also did not find a significant difference in MDA-LDL levels between patients with AF recurrence and those with sustained SR after a median follow-up of 9.7 years (Kimura *et al.* 2014). However, we did observe increased levels of Gal-3 and its association with MPO, both of which play a significant role in OxS development (Delporte *et al.* 2013; Lubrano and Balzan 2020). MPO targets apolipoprotein B-100, a unique protein of LDL, leading to the formation of myeloperoxidase-oxidized lipoproteins (Mox-LDL). Mox-LDL has been shown to activate endothelial cells and induces pro-inflammatory molecules, such as tumor necrosis factor  $\alpha$  and interleukin 8, thereby triggering inflammation (Delporte *et al.* 2013). Gal-3 has been found to enhance the expression of lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) in endothelial cells. LOX-1 is the primary receptor involved in the uptake of oxLDL, contributing to endothelial dysfunction caused by oxLDL (Ou *et al.* 2019).

Our study did not find a significant increase in MDA-LDL levels in patients with AF. However, the observed increase in Gal-3 suggests that other markers of OxS, such as Mox-LDL and LOX-1, may play a more critical role in the early development of AF. Therefore, future studies examining the relationship between OxS and AF should focus on these markers.

### 6.2.1. Limitations

There are some limitations to the current study that need to be addressed. One limitation is the relatively small sample size, which might have restricted the statistical power of the study. Additionally, since the patients were only periodically followed up, it is possible that some asymptomatic clinical AF recurrence episodes may have been missed. Another potential confounding factor is the use of different rhythm control strategies (PVI vs. cardioversion), which may have had an impact on the maintenance rate of SR, in addition to AF type and LA size. Future prospective studies should aim to investigate the predictive value of identified biomarkers for each subtype of AF and for each treatment strategy.

### 6.3. Anticoagulation of $\geq 65$ -year-old patients with atrial fibrillation and its impact on survival in Estonia (Paper III)

Paper III presented an overview of OAC use trends among  $\geq 65$ -year-old patients with AF and the impact of persistence of OAC use on survival. We found that persistent OAC use is still lacking in Estonia and that lower LDC with OACs was associated with lower survival during the one-year follow-up period.

The risk of stroke is significantly increased in patients with AF (Pistola *et al.* 2016; Healey *et al.* 2020; Migdady *et al.* 2021), and the main strategy for preventing stroke in this population is anticoagulation (Schwammenthal *et al.* 2011; Díez-Manglano *et al.* 2014; Jame and Barnes 2020; Imberti *et al.* 2022).

Our findings revealed that cohort I and cohort II had at least one OAC prescription in 77.7% and 68.6%, respectively, of all AF patients aged  $\geq 65$  years. This overall use of OACs is in line with data from the GARFIELD-AF and ORBIT-AF II registries, which reported OAC usage in 69% and 87% of patients with  $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$ , respectively (Steinberg *et al.* 2017; Bassand *et al.* 2021).

Nevertheless, self-reported data, which are utilized in several registries, have several limitations (Sevilla-Cazes *et al.* 2017). The accuracy of such data tends to decline with extended periods of observation (Stirratt *et al.* 2015), and the results from studies on other medications have indicated both over- and underestimation of real-world usage (Larsen *et al.* 2021). To obtain a more accurate estimation of tablet use, other technologies have been developed, such as electronic tablet dispensers (Parker *et al.* 2007; Eisenberger *et al.* 2013) and QR-code-based monitoring (Capranzano *et al.* 2021). However, these methods are primarily appropriate for small-scale clinical trials and are unsuitable for monitoring the entire population (Lam and Fresco 2015).

In terms of LDC analysis, only 57.4% of patients in cohort I and 44.5% of patients in cohort II were prescribed OACs that covered at least 80% of the days alive. As NOACs are fast-acting, short-lasting drugs with a half-life ranging from 5 to 17 hours on average (Heidbuchel *et al.* 2015), patients who miss recommended doses or experience interruptions in their continuous treatment may be at an increased risk of stroke (Capiou *et al.* 2020; Komen *et al.* 2020). Thus, aiming

for 100% LDC of prescriptions would be optimal, although studies have found that minimum effective coverage should be no less than 80% for some NOACs (Capiou *et al.* 2020). In this study, only 33.4% and 23.3% of patients in cohorts I and II, respectively, achieved 100% coverage, indicating a clear need for further interventions and patient and healthcare provider education to achieve higher coverage rates.

The two cohorts exhibited a statistical variance in mean age primarily attributed to the substantial sample size and slight differences in mean and standard deviation. However, these variations hold no clinical significance. In cohort II (2020), we observed a higher number of patients with concomitant renal insufficiency and coronary stents but a lower prevalence of HT.

The study identified a marked increase in the use of a single OAC and a decrease in the use of two or three different OACs in cohort II compared to cohort I. The reduction in warfarin prescriptions suggested that the changes observed were likely due to a shift from warfarin to NOACs and their wider availability (Grymonprez *et al.* 2022).

However, some differences were observed between the LDC groups. Although the patients in the 0% groups were statistically older, the difference was minor. Additionally, a higher prevalence of previously diagnosed stroke was observed in the 0% groups in cohort I. It is plausible that the absence of OACs in patients with a previous stroke is due to concerns about hemorrhagic events. However, it is also well established that a previous stroke is a significant risk factor for recurrent stroke (Khanevski *et al.* 2019), underscoring the need for careful evaluation of OAC use or the withholding of treatment (Hindricks *et al.* 2021). Furthermore, a higher prevalence of cancer diagnosis was seen in the population where no OACs were prescribed in cohort I. Given that real contraindications for OAC use could not be assessed in this study, the reasons for lower OAC use among cancer patients remain unclear. This may be due to the use of low molecular weight heparin in this group, concerns about bleeding, or the frailty of the patients.

We observed a lower prevalence of HT in the groups where no OACs were prescribed compared to those receiving OACs. This could be attributed to the lower perceived risk of stroke among patients without comorbidities of HT. However, the high prevalence of HT (84.9% and 84.6%) in the 0% OAC groups of both cohorts suggests that the reasons why these patients did not receive anticoagulation remain unclear. A lower prevalence of diabetes was also seen in the 0% LDC group in cohort I.

Our study results showed that patients in the LDC 0% groups had significantly lower observed and relative survival rates compared to patients in other LDC groups, indicating the potential beneficial effects of OAC use on survival in these patients. It should be emphasized that no causal claims can be made regarding survival differences from this study because of the design of the study. Still, these findings coincide with other studies looking at persistent use of OACs, which show a decrease of all-cause mortality in patients with persistent use of OACs compared to non-persistent patients (Toorop *et al.* 2021).

In our research, we propose an easily applicable approach for characterizing and evaluating the persistent usage of OACs in stroke prevention. By utilizing LDC analysis, we can obtain a precise estimation of the real-world application of these drugs. The comprehensive coverage of the Estonian Digital Medical Prescription Centre's database, which contains data for more than 99% of all prescriptions (e-Estonia 2022), allows us to study the entire Estonian population of 1.33 million (Statistics Estonia 2022).

Adherence to OAC therapy tends to decrease over time (Banerjee *et al.* 2020), which has been associated with an increased risk of stroke (Komen *et al.* 2020). To improve OAC use, one potential strategy could be the continuous or on-demand assessment of LDC by their family physician. As the Estonian Medical Prescription Centre's database can be accessed by various medical software in Estonia, an integrated tool that alerts the physician or nurse when a patient's LDC falls below the threshold could facilitate the scheduling of a visit or remote consultation to renew the prescription. Such a system could also be applied to other medications that require regular intake, such as anti-hypertensive or glycoselowering drugs. Studies involving smartphone apps for prescription renewal reminders and educational materials have shown promise in improving adherence to OAC therapy in patients with AF (Turakhia *et al.* 2021; Senoo *et al.* 2022).

Upon examining the relationship between prescribed and dispensed medications, we discovered that the majority of prescribed drugs were also dispensed. This suggests that the primary reason for the low LDC is likely the low prescribing rate by physicians. Integrating patients' LDC data in a simple and accessible way into daily clinical practice could potentially enhance long-term persistence to OAC therapy and other medications.

### 6.3.1. Limitations

This study has several limitations that require acknowledgment. Firstly, due to the lack of information on true contraindications to OAC therapy, we may have overestimated the proportion of patients in the 0% groups who should have received OAC therapy. Additionally, there might have been patients in the 0% category who were utilizing low molecular weight heparin for stroke prevention. Secondly, INR monitoring data was not accessible to us, so we were unable to evaluate the time in the therapeutic range for warfarin use to obtain an accurate estimation of proper dosing. Lastly, as our study focused on prescribed LDC, the true estimate of the individual patients' drug adherence remains beyond the scope of the present study and may influence survival rates.

## 7. CONCLUSIONS

1. Patients with a history of atrial fibrillation had higher central systolic blood pressure and central pulse pressure compared to the control group, even when peripheral blood pressures were similar and patients were in sinus rhythm. Our results suggest that central blood pressure assessment might improve the residual cardiovascular risk assessment of these patients.
2. Atrial fibrillation is linked to increased pulse wave velocity in patients with paroxysmal and persistent atrial fibrillation, indicating increased arterial stiffness. Our study supports the role of arterial stiffness in the development of the arrhythmia and hints at a potential treatment target for prevention of the disease.
3. Patients with atrial fibrillation had significantly higher levels of N-terminal pro-brain natriuretic peptide and galectin-3 compared to the control group. These findings indicate the role of inflammatory processes and the development of fibrosis as pathophysiological mechanisms in the development of atrial fibrillation.
4. Baseline myeloperoxidase was an independent prognostic marker for arrhythmia recurrence irrespective of rhythm control strategy (cardioversion or pulmonary vein isolation). This finding once again illustrates the role of fibrosis in the processes leading to atrial fibrillation. Myeloperoxidase may serve as a novel prognostic marker for atrial fibrillation recurrence and help to choose individualized treatment strategies.
5. Lifeday coverage  $\geq 80\%$  with oral anticoagulation was 57.4% in cohort I and 44.5% in cohort II in patients aged  $\geq 65$  years for the one-year follow-up. Our study shows that while many patients are starting oral anticoagulation therapy for stroke prevention, the long-term treatment persistence is insufficient and needs improvement in Estonia.
6. Lifeday coverage with oral anticoagulation correlates with observed and relative survival rates in patients with atrial fibrillation aged  $\geq 65$  years during the one-year follow-up period. The lowest survival rates were seen in patients without anticoagulation. These findings indicate a positive net benefit of anticoagulation in patients aged  $\geq 65$  for atrial fibrillation-related stroke prevention.

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## 9. SUMMARY IN ESTONIAN

### Kodade virvendusarütmiaga patsientide hemodünaamiline ja biokeemiline profiil ning $\geq 65$ aastaste kodade virvendusarütmiaga patsientide antikoagulantravi Eestis

Kodade virvendusarütmiat on sagedaseim rütmihäire maailmas esinedes 2–4% täiskasvanutest. Selle rütmihäire esinemissagedus on kasvamas ja järgnevatel kümnenditel on oodata selle 2,3-kordset tõusu.

Kodade virvendusarütmiat patofüsioloogilised mehhanismid on keerulised ja pole praeguseni täielikult selged. Teada on seos vanusega, elustiili ning kaasnevate haigustega, kuid antud rütmihäiret mõjutavad ka mitmed geneetilised faktorid. Kõige olulisemaks muudetavaks riskifaktoriks on jätkuvalt hüpertensioon.

Kuigi õlavarrelt mõõdetud perifeerset vererõhku kasutatakse standardselt vererõhu hindamiseks, on uuringud näidanud, et vererõhk aordis (tsentraalne vererõhk) võib oluliselt erineda perifeerselt vererõhust. Need erinevused tulenevad arterite jäikusest ja fenomenist mida nimetatakse pulsiline amplifikatsiooniks. Arterite jäikus ja tsentraalne vererõhk korreleeruvad uuringute alusel paremini kardiovaskulaarse riskiga, kui perifeerne vererõhk. Lisaks on teada, et erinevad vererõhku mõjutavad ravimid langetavad perifeerset ja tsentraalset vererõhku erineval määral ning kodade virvendusarütmiaga patsientidel laialdaselt kasutatavad beeta-blokaatorid ei pruugi nii efektiivselt langetada tsentraalset vererõhku kui teised preparaadid. See omakorda võib seletada kodade virvendusarütmiaga patsientide suuremat kardiovaskulaarset riski.

Kodade virvendusarütmiaga patsientidel esinevad muutused südames nii rakulisel, kui ka koe tasandil, mis soodustavad rütmihäire püsimist. Tekib nii elektriline, kui ka ehituslik remodelleerumine kodades. Uuringud viitavad, et selles protsessis on olulisel kohal nii põletik, kui ka oksüdatiivne stress, mis viivad kodade fibroosini, mida peetakse oluliseks rütmihäireid soodustavaks teguriks.

Kodade virvendusarütmiaga patsientidel on kuni 5 korda kõrgem risk ajuinsuldiks, kuid risk on väga heterogeenne ja sõltub kaasnevatest haigustest ning riskifaktoritest. Kõrge riskiga patsiendid ( $CHA_2DS_2-VASc \geq 2$ ) peaksid tarvutama eluaegset trombemboolia profülaktikat suukaudsete antikoagulantidega. Kuigi tegemist on efektiivsete ravimitega näitavad suured registrid, et antikoagulantravi on jätkuvalt alakasutatud. Registreid, mis hindaks antikoagulantravi kasutust Eestis ei ole.

## **Uurimistöö eesmärgid**

Käesoleva uurimistöö üldiseks eesmärgiks on kirjeldada kodade virvendusarütmiaga patsientide tsentraalset hemodünaamikat kajastavaid parameetreid ja hinnata muutuseid põletikku, oksüdatiivset stressi ning fibroosi kajastavates biomarkerites. Lisaks kirjeldada antikoagulantravi kasutamist ajuinsuldi profülaktikaks  $\geq 65$  aastastel kodade virvendusarütmiaga patsientidel Eestis.

## **Uurimistöö spetsiifilised eesmärgid:**

1. Hinnata kodade virvendusarütmiaga patsientide tsentraalset vererõhku võrreldes kontrollgrupiga.
2. Hinnata kodade virvendusarütmiaga patsientide pulsilaine levikukiirust võrreldes kontrollgrupiga.
3. Kirjeldada põletiku, fibroosi ja oksüdatiivse stressiga seotud markerite väärtusi kodade virvendusarütmiaga patsientidel.
4. Anda informatsiooni põletiku, fibroosi ja oksüdatiivse stressiga seotud markerite seostest kodade virvendusarütmiaga episoodide kordumisega üheaastase jälgimisperioodi jooksul
5. Kirjeldada antikoagulantravi trende  $\geq 65$  aastastel kodade virvendusarütmiaga patsientidel Eestis aastatel 2019 ja 2020.
6. Hinnata eluspäevade kaetust antikoagulantraviga ja selle seoseid ühe aasta suremusega  $\geq 65$  aastaste kodade virvendusarütmiaga patsientide seas Eestis aastatel 2019 ja 2020.

## **Patsiendid ja meetodid**

Uurimistöö biomarkerite ja tsentraalse hemodünaamikaga seotud uuringusse kaasati paroksüsmaalse ja persisteeruva kodade virvendusarütmiaga patsiendi (biomarkerite uuringus 76 patsienti, tsentraalse hemodünaamika uuringus 75 patsienti), kes hospitaliseeriti kodade virvendusarütmiaga kardioversiooniks Tartu Ülikooli Kliinikumi või kodade virvendusarütmiaga kateeterablatsioonraviks Põhja-Eesti Regionaalhaiglasse. Kontrollgrupiks oli 75 vanuse ja soo alusel kohandatud tervet uuringualust.

Uuritavatel määrati enne protseduure põletiku, oksüdatiivse stressi ja fibroosiga seotud markereid Tartu Ülikooli Kliinikumi Ühendlaboris ja Tartu Ülikooli bio- ja siirdemeditsiini instituudi biokeemia osakonnas. Kardioversiooniga siinusrütmi taastatud patsientidel määrati ühe ööpäeva jooksul arterite jäikust pulsilaine kiiruse alusel ja tsentraalset vererõhku pulsilaine analüüsi abil (Sphygmocor XCEL, AtCor Medical) Tartu Ülikooli Kardioloogiakliiniku Endoteeli Keskuses. Samad mõõtmised tehti siinusrütmiaga patsientidel enne kodade virvendusarütmiaga kateeterablatsioonravi Põhja-Eesti Regionaalhaigla Kardioloogiakeskuses.

Antikoagulantravi trendide hingamiseks koostati Eesti Haigekassa andmebaasist isikustamata patsientide nimekiri kõigist  $\geq 65$  aastastest kodade virvendusarütmia patsientidest, kellel esines uuringueelsel aastal kodade virvendusarütmia diagnoos. Andmed seoti Eesti Haigekassa Retseptikeskuse ja Surmaregistri andmebaasidega, hindamaks üheaastase uuringuperioodi jooksul (või kuni patsiendi surmani) antikoagulantravi väljakirjutamist. Kõigil patsientidel hinnati eluspäevade kaetust antikoagulantravi väljakirjutatud doosidega, mis on näidustatud kodade virvendusarütmia patsientidel trombiprofülaktilikaks vastavalt kehtivatele ravijuhenditele. Eluspäevade kaetust väljendati protsendina päevadest üheaastase perioodi kohta (või kuni patsiendi surmani), mida katavad väljakirjutatud antikoagulantravi päevadoosid. Lisaks hinnati ka antikoagulantravi retseptide väljakirjutamise ja väljaostmise seoseid. Surmaregistri andmete alusel hinnati uuritava patsientide üldsusemust registri põhiselt ja sama vanusegrupi üldsusemust uuringuperioodidel.

### Uurimistöö tulemused ja järeldused

1. Kodade virvendusarütmia patsientidel oli kõrgem tsentraalne süstoolne vererõhk ja tsentraalne pulsirõhk võrreldes tervete kontrollgrupiga. Samas ei erinenud gruppide vahel perifeersed vererõhu väärtused. Antud tulemused viitavad, et tsentraalse vererõhu mõõtmine võiks parandada kodade virvendusarütmia patsientide kardiovaskulaarse riski ja subkliinilise organkahjustuse hindamist.
2. Kodade virvendusarütmia on seotud kõrgema pulsilaine levikukiirusega paroksüsmaalse ja persisteeruva rütmihäirega patsientidel, viidates kõrgeenenud arterite jäikusele. Meie uuring kinnitab arterite jäikuse rolli kodade virvendusarütmia kujunemises ja viitab potentsiaalsele ravisihmürgile, mis võiks olla oluline rütmihäire preventtsioonis.
3. Kodade virvendusarütmia patsientidel olid oluliselt kõrgemad B-tüüpi natriureetilise propeptiidi N-fragmendi ja galektiin-3 väärtused võrreldes kontrollgrupiga. Need tulemused näitavad põletikuprotsesside tähtsust fibroosi kujunemisel, mis on oluline patofüsioloogiline mehhanism kodade virvendusarütmia tekkes.
4. Müeloperokside baasväärtuste määramine oli iseseisev prognostiline marker korduva rütmihäire tekkeks sõltumata valitud rütmikontrolli strateegiast (kardioversioon või kodade virvendusarütmia kateeterablatsioon). Müeloperokside võiks olla potentsiaalne prognostiline marker kodade virvendusarütmia taastekke riski hindamisel ja aidata valida individualiseeritud ravistrateegiat patsientidele.

5. Eluspäevade kaetus  $\geq 80\%$  antikoagulantraviga oli kohordis I 57,4% ja kohordis II 44,5%,  $\geq 65$  aastaste kodade virvendusarütmiaga patsientide seas üheaastase jälgimisperioodi jooksul. Meie uuring kinnitab, et kuigi paljud patsiendid alustavad insuldiprofülaktikat antikoagulantidega, siis pikaajaline ravi on Eestis ebapiisav ja vajab edendamist.
6. Eluspäevade kaetus antikoagulandiga on seotud elulemusega  $\geq 65$  aastaste kodade virvendusarütmiaga patsientide seas üheaastase jälgimisperioodi jooksul. Kõige madalam elulemus on ilma antikoagulantravita patsientide seas. Need tulemused viitavad summaarselt positiivsele kasu-kahtluse suhtele antikoagulantravi kasutamisel  $\geq 65$  aastaste kodade virvendusarütmiaga patsientide seas trombi profülaktikaks.

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## **11. PUBLICATIONS**

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01.06.2019– Tartu University Hospital, Department of Arrhythmias, cardiologist, as of 01.05.2023 senior cardiologist  
01.05.2017– University of Tartu, Institute of Clinical Medicine, Department of Cardiology, Assistant  
01.09.2015– University Hospital, Department of Cardiology 1, cardiologist, as of 01.05.2023 senior cardiologist

### Professional associations:

2022– Estonian Society of Hypertension, President  
2017–2022 European Heart Rhythm Associations Young Electrophysiologist Working Group, National Ambassador of Estonia  
2017– Estonian Society of Cardiology, Working Group of Arrhythmias, member  
2016–2022 Estonian Society of Hypertension, secretary  
2016– Estonian Society of Hypertension, board member  
2015– European Society of Hypertension, member  
2015– Estonian Society of Hypertension, member  
2014– European Heart Rhythm Association, member  
2011– Estonian Society of Cardiology, member  
2011– Estonian Society of Cardiology, Working Group of Young Cardiologists, member

### Professional development:

2018–2023 International electrophysiology fellowship “Abbott Interventional EP Curriculum”, different countries in Europe  
2018 International course “OMI Salzburg Cardiology seminars”, Austria  
2016 International conference “ARTERY 2016”, Denmark  
2015 European Society of Hypertension Summer School, Austria  
2013 International conference “The Cardiovascular Disease Continuum in the Era of Evidence Based Medicine”, Estonia

**Scientific work:**

My main research interests are the hemodynamic profile and biomarkers related to oxidative stress, fibrosis, and inflammation in patients with atrial fibrillation and the use of oral anticoagulants for the prevention of thromboembolic events in patients with atrial fibrillation.

**Publications in international peer-reviewed journals:**

- Pauklin P, Marandi T, Kals M, et al. Lifeday coverage of oral anticoagulants and one-year relative survival in patients with atrial fibrillation: a population-based study in Estonia. *BMC Cardiovasc Disord.* 2023;23(1):398.
- Mancia G, Kreutz R, Brunström M, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *J Hypertens.* 2023;41(12):1874-2071.
- Pauklin P, Zilmer M, Eha J, et al. Markers of Inflammation, Oxidative Stress, and Fibrosis in Patients with Atrial Fibrillation. *Oxid Med Cell Longev.* 2022; 2022:4556671.
- Pauklin P, Eha J, Tootsi K, et al. Atrial fibrillation is associated with increased central blood pressure and arterial stiffness. *J Clin Hypertens (Greenwich).* 2021;23(8):1581–1587.
- Potpara TS, Lip GYH, Dargès N, et al. Cohort profile: the ESC EURObservational Research Programme Atrial Fibrillation III (AF III) Registry. *Eur Heart J Qual Care Clin Outcomes.* 2021;7(3):229–237.
- Pauklin, P. Krooniline südamepuudulikkus ja diabeet. *Eesti Arst.* 2019;98(LISA 1): 67–73.
- Schernthaner G, Lotan C, Baltadzhieva-Trendafilova E, Pauklin P et al. Unrecognised cardiovascular disease in type 2 diabetes: is it time to act earlier?. *Cardiovasc Diabetol.* 2018;17(1):145.
- Pauklin P, Kampus P. Euroopa Kardioloogide Seltsi 2016. aastal avaldatud ravijuhendi “Kodade virvendusarütmia käsitus” tutvustus. *Eesti Arst.* 2016; 95(11):737–741

## ELULOOKIRJELDUS

**Nimi:** Priit Pauklin  
**Sünniaeg:** 06.10.1985, Jõgeva, Eesti  
**Kodakondsus:** Eesti  
**Telefon:** +372 528 4692  
**E-post:** Priit.Pauklin@gmail.com; Priit.Pauklin@kliinikum.ee

### Haridus:

2015–2023 Doktorantuur, Tartu Ülikooli arstiteaduskond  
2010–2015 Residentuur (kardioloogia), Tartu Ülikooli arstiteaduskond  
2004–2010 Arstiteadus, Tartu Ülikooli arstiteaduskond  
1992–2004 Jõgeva Gümnaasium

### Erialane teenistuskäik:

01.06.2019– SA Tartu Ülikooli Kliinikum, Rütmihäirete osakond, arst-õppejõud kardioloogia erialal, alates 01.05.2023 vanemarst-õppejõud kardioloogia erialal  
01.05.2017– Tartu Ülikool, Südamekliinik, kardioloogia assistent  
01.09.2015– SA Tartu Ülikooli Kliinikum, 1. Kardioloogia osakond, arst-õppejõud kardioloogia erialal, alates 01.05.2023 vanemarst-õppejõud kardioloogia erialal

### Erialane kuuluvus:

2022– Eesti Hüpertensiooni Ühing, President  
2017–2022 Euroopa Rütmihäirete Assotsiatsiooni Noorrütmoloogide töögrupp, Eesti esindaja  
2017– Eesti Kardioloogide Seltsi Rütmihäirete töögrupp, liige  
2016–2022 Eesti Hüpertensiooni Ühing, sekretär  
2016– Eesti Hüpertensiooni Ühing, juhatuse liige  
2015– Euroopa Hüpertensiooni Ühing, liige  
2015– Eesti Hüpertensiooni Ühing, liige  
2014– Euroopa Rütmihäirete Assotsiatsioon, liige  
2011– Euroopa Kardioloogide Selts, liige  
2011– Eesti Kardioloogide Seltsi Noorkardioloogide töögrupp, liige

### Erialane täiendus:

2018–2023 Rahvusvaheline elektrofüsioloogide koolitusprogramm “Abbott Interventional EP Curriculum”, koolitusprogramm erinevates riikides  
2018 Rahvusvaheline kursus “OMI Salzburg Cardiology seminars”, Austria  
2016 Rahvusvaheline konverents “ARTERY 2016”, Taani  
2015 Euroopa Hüpertensiooni Ühingu suvekool, Austria  
2013 Rahvusvaheline konverents “The Cardiovascular Disease Continuum in the Era of Evidence Based Medicine”, Estonia

**Teadustegevus:**

Teadustöö põhisuundadeks on hemodünaamika, oksüdatiivse stressi, fibroosi ja põletikumarkerite uurimine kodade virvendusarütmiaiga patsientidel ning anti-koagulantravi kasutamise hindamine kodade virvendusarütmiaiga patsientide trombiprofülaktilikaks.

**Artiklid rahvusvahelistes eelretsenseeritavates ajakirjades:**

Pauklin P, Marandi T, Kals M, et al. Lifeday coverage of oral anticoagulants and one-year relative survival in patients with atrial fibrillation: a population-based study in Estonia. *BMC Cardiovasc Disord.* 2023;23(1):398.

Mancia G, Kreutz R, Brunström M, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *J Hypertens.* 2023;41(12):1874–2071.

Pauklin P, Zilmer M, Eha J, et al. Markers of Inflammation, Oxidative Stress, and Fibrosis in Patients with Atrial Fibrillation. *Oxid Med Cell Longev.* 2022; 2022:4556671.

Pauklin P, Eha J, Tootsi K, et al. Atrial fibrillation is associated with increased central blood pressure and arterial stiffness. *J Clin Hypertens (Greenwich).* 2021;23(8):1581–1587.

Potpara TS, Lip GYH, Dagues N, et al. Cohort profile: the ESC EURObservational Research Programme Atrial Fibrillation III (AF III) Registry. *Eur Heart J Qual Care Clin Outcomes.* 2021;7(3):229–237.

Pauklin, P. Krooniline südamepuudulikkus ja diabeet. *Eesti Arst.* 2019;98 (LISA 1): 67–73.

Schernthaner G, Lotan C, Baltadzhieva-Trendafilova E, Pauklin P et al. Unrecognised cardiovascular disease in type 2 diabetes: is it time to act earlier?. *Cardiovasc Diabetol.* 2018;17(1):145.

Pauklin P. Kampus P. Euroopa Kardioloogide Seltsi 2016. aastal avaldatud ravi-juhendi “Kodade virvendusarütmia käsitus” tutvustus. *Eesti Arst.* 2016; 95(11):737–741

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