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Clinical evaluation and implications of left atrial remodeling in atrial fibrillation

From silent cerebral lesions and atrial stunning to novel electrocardiographic tools for prediction of arrhythmia outcome

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Abstract

Arvanitis, P. 2023. Clinical evaluation and implications of left atrial remodeling in atrial fibrillation. From silent cerebral lesions and atrial stunning to novel electrocardiographic tools for prediction of arrhythmia outcome. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1949. 92 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-1816-5.

Atrial fibrillation (AF) is the most common cardiac arrhythmia. Left atrial (LA) remodeling and reverse remodeling are associated with cerebral involvement and cognitive function (CF) changes. Risk stratification for AF related outcomes is essential in the management of patients with AF.

This thesis aimed to 1) explore the effects of AF in a prospective cohort of anticoagulant-naïve patients, who underwent cardioversion (CV) within 48 hours after debut (Studies I and II) on i) occurrence of new silent thromboembolic events using brain magnetic resonance imaging, CF, cerebral biomarker ii) atrial remodeling and thrombogenicity using echocardiography, and hypercoagulability biomarkers; 2) identify novel electrocardiographic (ECG) predictors of 12-months AF recurrence, (Study III), in patients with non-permanent AF after CV or pulmonary vein isolation and study its effect on reverse atrial electrical remodeling (RAER) and 3) to evaluate traditional and novel ECG- and clinical predictors of new-onset AF (new-o-AF) on hospitalized Covid-19 patients (Study IV) and explore the impact of AF on clinical outcomes.

In Papers I and II, acute silent cerebral lesions could not be identified. A higher incidence of white matter hyperintensities was associated with higher CHA2DS2-VASc-score. A transient increase in cerebral damage biomarker was observed. Persistent AF patients had inferior CF test results. LA stunning resolved within ten days. The reverse functional remodeling was incomplete in patients with AF history. Higher levels of hypercoagulability-related biomarkers were observed prior to CV.

In Paper III, the novel Peq-time>33ms, from P-wave onset to the peak positive deflection, independently predicted 12-months AF recurrence. The P-leftward-area, from peak positive deflection to the offset of P-wave, showed the largest change during follow-up, describing RAER. Machine-learning predictive model including variables from the novel P-wave partitioning showed the best predictive performance.

In Paper IV, the novel Peq-time>33ms, PR-interval>190ms and P-wave-duration>115ms were independent predictors of n-o-AF. Admission to the intensive care unit (ICU), need for respiratory support, advanced age, males and increased body mass index (BMI) independently predicted new-o-AF. Logistic regression predictive models including age, sex, BMI, ICU admission and Peq-time or PR-interval had the best balanced accuracy.

In conclusion, our findings in Studies I and II might suggest an enhanced thrombogenicity, even in patients with low stroke risk, supporting the concept of anticoagulation pericardioversion. We introduced the novel Peq-time, independently predicting AF recurrence in Study III and, along with PR-interval, new-o-AF in Study IV. Predictive models of arrhythmia outcome could be implemented in individually-tailored AF management and surveillance.

Keywords: Atrial fibrillation, left atrial remodeling, recurrence, new-onset, silent cerebral lesions, white matter hyperintensities, cardioversion, pulmonary vein isolation, risk factors, electrocardiographic predictors, P-wave indices, machine learning, predictive models, Covid-19

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To my beautiful family, my dream team…

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. Arvanitis P, Johansson AK, Frick M, Malmborg H, Gerovasileiou S, Larsson EM, Blomström-Lundqvist C. Serial Magnetic Resonance Imaging after Electrical Cardioversion of Recent Onset Atrial Fibrillation in Anticoagulant-Naïve Patients - A Prospective Study Exploring Clinically Silent Cerebral Lesions. *J Atr Fibrillation.* 2020 Aug 31;13(2):2271. doi: 10.4022/jafib.2271

II. Arvanitis P, Johansson AK, Frick M, Malmborg H, Gerovasileiou S, Larsson EM, Blomström-Lundqvist C. Recent-onset atrial fibrillation: a study exploring the elements of Virchow's triad after cardioversion. *J Interv Card Electrophysiol.* 2022 Jun;64(1):49-58. doi: 10.1007/s10840-021-01078-9

III. Panagiotis Arvanitis, David Mörtsell, Carina Blomström-Lundqvist. (2023) Novel P-wave indices and machine learning predict atrial fibrillation recurrence after rhythm control interventions. *Submitted*

IV. Panagiotis Arvanitis, Tor Biering-Sørensen, Cecilia Linde, Helena Malmborg, Jeanne E. Poole, Arun R. Sridhar, Patrick M. Boyle, Carina Blomström-Lundqvist. (2023) Risk factors and electrocardiographic predictors associated with new-onset atrial fibrillation in hospitalized Covid-19 patients. Evaluation of a novel P-wave index. *Submitted*

Contents

Abbreviations

AAD	Antiarrhythmic Drugs
AF	Atrial fibrillation
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
Covid-19	Corona virus disease 2019
CoxR	Cox proportional hazards regression
CV	Cardioversion
DM	Diabetes mellitus
ECG	Electrocardiography
ESC	European Society of Cardiology
HF	Heart Failure
hs-cTNT	High-sensitivity cardiac troponin T
HT	Hypertension
ICU	Intensive care unit
IL-6	Interleukin 6
LA	Left Atrium/Atrial
LOS	Length of stay
MRI	Magnetic resonance imaging
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New-York Heart Association
OAC	Oral anticoagulant
PTf1+2	Prothrombin fragment 1+2
PVI	Pulmonary vein isolation
PWD	P-wave duration
PwTfV1	P-wave terminal forces in lead V1
QoL	Quality of Life
RAER	Reverse atrial electrical remodeling
RCI	Reliable Change Index
S100b	S100 calcium-binding protein B
vWFag	von Willebrand Factor antigen
WMH	White Matter T2 Hyperintense lesions

1. Introduction

1.1 Historical aspects of atrial fibrillation

'When the pulse is irregular and tremulous and the beats occur at intervals, then the impulse of life fades' wrote the Yellow Emperor of China (Huang Ti Nei Ching Su Wen) in his Classics of Internal Medicine, in the 27th-25th century BC.[1] In retrospect, he was probably describing atrial fibrillation (AF) for the first time. In 1628, William Harvey first described 'auricular fibrillation' in animals and Jean-Baptiste de Senac (1693-1770) associated AF with mitral valve disease.[2, 3] In 1785, William Withering discovered and popularized the medical use of digitalis leaf (digitalis purpurea).[1, 4] At the end of the 19th century, Willem Einthoven revolutionized cardiology with the invention of electrocardiography; AF is depicted among various single-lead ECG recordings and named as 'pulsus irregularis et inaequalis'.[5] In 1909 Sir Thomas Lewis first reported AF as 'Auricular Fibrillation: a common condition'.[6-8] In 1962-63 Lown and colleagues introduced cardioversion (CV) as a safer and more effective treatment of AF compared to quinidine.[9, 10] The beneficial use of anticoagulants against thromboembolism was initially reported in the 1960s and in the late 2000s introduced for the primary and secondary prevention of stroke.[11-13] The early theories of AF mechanisms, i.e. re-entry by William Withering, automaticity by sir Thomas Lewis and multiple wavelets by Gordon Moe, led to the development of invasive AF treatments, from the Maze surgical procedure developed by J.L. Cox to the catheter ablation procedures, introduced by M. Haïssaguerre, opening a new era to the invasive treatment of AF.[2, 14-18]

1.2 Definition and prevalence of atrial fibrillation

AF is defined as a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction, having the following electrocardiographic (ECG) characteristics: (i) irregularly irregular R-R intervals (when atrioventricular conduction is not impaired), (ii) absence of distinct repeating P waves and (iii) irregular atrial activations.[19] Clinical AF refers to any symptomatic or asymptomatic AF documented by an ECG tracing for at least 30 seconds (s) or the entire 12-lead ECG. Subclinical AF refers to individuals without clinical AF or symptoms attributable to AF, but with

atrial high-rate episodes, as detected by a cardiac implantable electronic device or an implantable/wearable cardiac monitor and confirmed to be AF, atrial flutter or atrial tachycardia.[19]
Five patterns of AF are distinguished, based on presentation, duration, and spontaneous termination of AF episodes (Table 1).[19]

Table 1. Classification of AF

AF pattern	Definition
First diagnosed	AF not diagnosed before (also called new-onset AF)
Paroxysmal	AF that terminates spontaneously or with intervention within 7 days of onset
Persistent	AF that is continuously sustained beyond 7 days, including episodes terminated by cardioversion (drugs or electrical cardioversion) after > 7 days
Long-standing persistent	Continuous AF of >12 months, when deciding to adopt a rhythm control strategy.
Permanent	AF that the patient and physician accept, and no further attempts to restore/maintain sinus rhythm will be undertaken

AF is the most common sustained arrhythmia in adults.[20] The prevalence of AF is on the rise, increasing 3-fold over the past 50 years and has been estimated between 2-4% globally.[21, 22] In Europe, among individuals >55 years, the prevalence of AF was ≈ 9 million in 2010 and estimated to reach ≈14 million by 2060.[23, 24] With improved survival of chronic conditions and increased average life expectancy, AF has become a 21st-century cardiovascular epidemic.[20, 21] Besides in advanced age, a higher prevalence of AF is observed in patients with hypertension (HT), diabetes mellitus (DM), heart failure (HF), renal failure, obesity, obstructive sleep apnea (OSA), excessive alcohol consumption, smoking and sedentary lifestyle or extreme exercise.[25-37] Female sex and non-Caucasian ethnicity are associated with a lower prevalence of AF.[38-42]

1.3 Atrial fibrillation-related clinical outcomes

1.3.1 Symptoms

AF symptomatology varies greatly, from asymptomatic AF, accounting for about one third of the patients to highly symptomatic and disabling resulting in poor quality of life (QoL).[19, 43] The chief complains of AF patients include rapid and irregular heartbeat, general fatigue, fluttering or palpitations in the chest, dizziness, shortness of breath, anxiety, weakness, faintness or confusion, exercise fatigue, sweating, and chest pain or pressure. Symptom severity

is stratified according to the European Heart Rhythm Association (EHRA) symptom score (Table 2).[19]

Table 2. The EHRA symptom score

Score	Symptoms	Description
1	None	AF does not cause any symptoms
2a	Mild	Normal daily activity not affected by symptoms related to AF
2b	Moderate	Normal daily activity not affected by symptoms related to AF, but patient troubled by symptoms
3	Severe	Normal daily activity affected by symptoms related to AF
4	Disabling	Normal daily activity discontinued

The majority of AF patients (> 60%) have significantly impaired QoL and 16.5% have severe or disabling symptoms.[44] In women with AF, QoL is significantly lower as compared to men.[45] Factors associated with worse QoL were new-onset AF, higher heart rate, OSA, symptomatic HF, coronary artery disease, HT, chronic obstructive pulmonary disease and obesity.[46-48] Moreover, patients with AF have a higher burden of anxiety and depression.[49]

1.3.2 Stroke and systemic emboli

Chronic, non valvular AF patients had a 5-fold higher risk of stroke and systemic embolism, as compared to those without.[50] Intra-cardiac thrombus formation (cardioembolism), a result of abnormal blood flow and activated coagulation and inflammatory system[51], accounts for approximately one fifth of all ischemic strokes.[52] The duration of AF is positively associated with stroke risk: for episodes exceeding 5.5 hours (h) the stroke risk increased almost four times.[53] Moreover, subclinical AF longer than 6 minutes, detected by implanted cardiac devices, is associated with an increased risk of ischemic stroke and clinical AF.[54]

The attributed risk of AF for stroke is age-related; from 1,5% in the 6th decade to 23.5% in the 9th decade of life.[55] Because the risk of stroke in AF is modulated by other risk factors (e.g. age, HT, DM, previous thromboembolism, vascular disease, HF, sex), clinical management of primary and secondary stroke prevention is based on the well-established 'CHA_2DS_2-VASc' stratification score (Table 3a).[56] The annual unadjusted stroke risk rate for AF patients according to CHA_2DS_2-VASc score is shown in Table 3b.[56, 57]
Although the CHA_2DS_2-VASc score is used worldwide and has been well studied and validated, it might underestimate the risk in the group of patients classified in "the true low-risk category", 0-1, according to the CHA_2DS_2-VASc score.[58-60]

Table 3a. The CHA_2DS_2-VASc score

	Condition	Points
C	Congestive heart failure (or Left ventricular systolic dysfunction)	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A_2	Age ≥75 years	2
D	Diabetes Mellitus	1
S_2	Prior Stroke or Transient ischemic attack or thromboembolism	2
V	Vascular disease (peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (female sex)	1

Table 3b. Annual unadjusted stroke risk rate by CHA_2DS_2-VASc score

Score	Friberg 2012[57]	Lip 2010[56]
0	0.2	0.0
1	0.6	0.6
2	2.2	1.6
3	3.2	3.9
4	4.8	1.9
5	7.2	3.2
6	9.7	3.6
7	11.2	8.0
8	10.8	11.1
9	12.2	10.0

1.3.3 Clinically silent cerebral lesions

Clinically silent thromboembolic lesions have been reported in association with paroxysmal, persistent and permanent AF and mainly studied in relation to AF treatment with elective electrical CV or pulmonary vein isolation (PVI) with catheter ablation.[61-64] These lesions may occur even late after restoration of sinus rhythm, in the absence of intra-atrial thrombi prior to CV and can be attributed to the left atrial (LA) stunning and the slow process of atrial functional recovery.[62-64] Risk factors associated with silent cerebral infarction are age, HT, metabolic syndrome, carotid artery disease and renal failure.[65-67] However, acute silent thromboembolic lesion in patients with recent-onset AF, undergoing sub-acute CV, have not been studied.

Additional to lesions attributed to acute microemboli in the brain, chronic white matter T2 hyperintense lesions (WMH), detected by brain magnetic resonance imaging (MRI), are often considered sequelae of infection or inflammation in individuals younger than 50-60 years; however, there is growing evidence of clear association between AF and WMH.[68] Reportedly, WMH were observed in 56.4% of persistent AF patients prior to elective CV and in 67.6% paroxysmal AF patients prior to PVI.[69, 70] The CHA_2DS_2-Vasc score was an independent predictor for the presence of WMH and the Fazekas score[71] (quantitative grading score for WMH lesions) was positively correlated with the CHA_2DS_2-Vasc scores.[65] Figure 1 depicts brain MRI showing WMH based on Fazekas classification: Grade 0: no lesions (panel A), grade 1: punctuate foci (panel B), grade 2: beginning confluence (panel C), and grade 3: large confluent areas.

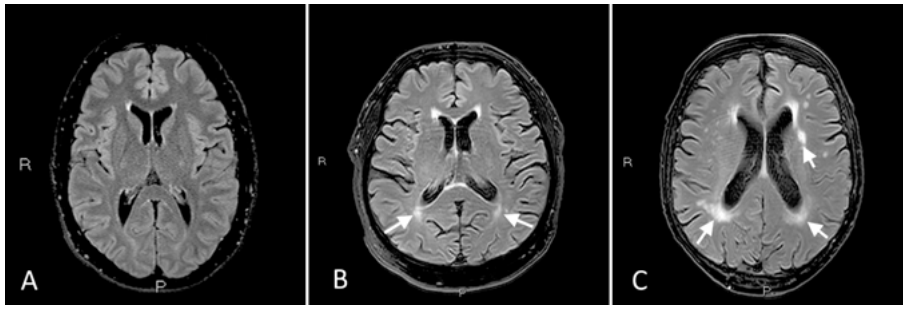

Figure 1. *WMH according to the Fazekas score*

1.3.4 Cognitive impairment

Cognitive decline is strongly linked to AF, sharing the common risk factor of increasing age.[72] The relative risk of cognitive impairment and dementia in AF has been reported at 1.3-1.8 times higher compared to controls.[73-75] A multifactorial mechanism underlies this association involving hypoperfusion (beat-to-beat variability and decreased cardiac output), activation of the inflammatory and coagulative systems, endothelial injury and circulatory stasis promoting thrombogenicity, resulting in covert thromboembolism, microthromboembolism or WMH lesions.[72, 76]

1.3.5 Heart failure

The incidence of first-diagnosed HF in the Framingham Heart Study in patients with AF was 33 per 1000 person-years.[34] Moreover, the incidence of congestive HF was markedly higher in participants with AF than the incidence of AF in those with antecedent HF, meaning that AF begets HF more than HF begets AF.[77] Among patients with AF, there is a higher risk of development

of heart failure with preserved left ventricular ejection fraction (LVEF), compare to the risk of developing HF with decreased LVEF.[77] Moreover, development of HF in the AF population was associated with an increased mortality in both men and women.[34]

1.3.6 Mortality

AF is associated with up to a 3.7-fold increased risk of all-cause mortality, compared with the general population.[78, 79] Of note, the survival advantage observed in women versus men disappeared in the presence of AF.[78]

1.4 Pathophysiology and atrial remodeling

1.4.1 Initiation and maintenance

AF is characterized by rapid and uncoordinated atrial electrical activity. The mechanisms underlying AF initiation and its maintenance are incompletely understood.[80, 81] Electrical re-entry following triggered activity acting on a vulnerable substrate give rise to AF.[82] Early afterdepolarizations and delayed afterdepolarizations are the main forms of triggered activity.[80] Ectopic beats, originating from the pulmonary vein , have been identified as the initiating trigger in paroxysmal AF.[83] Anatomic re-entry is mainly due to focal structural changes and fibrosis, while functional re-entry is related to reduction of conduction velocity or reduction of the effective refractory period in the atrial myocardium.[80, 84, 85] Action potential duration and refractory period are shorter in the atria, as compared to the ventricles, making atrial myocardium prone to the development of very rapid rates.[86]

After initiation of AF there is an intracellular calcium overload secondary to decreased inward L-type Ca^{2+} and Na^{+} current during depolarization and voltage-gated K^{+} currents during repolarization.[87, 88] This electrical remodeling results in shortening of the effective refractory period, reducing the action potential duration, promoting functional reentry.[89-91] As AF becomes more persistent, functional and later structural remodeling develops, promoting multiple reentry (wavelet) predominantly involved in the maintenance of AF.[92] Structural remodeling includes cardiomyocyte apoptosis, glycogen accumulation, replacement interstitial fibrosis and cardiomyocyte hypertrophy, leading to gradual enlargement and dysfunction, which promotes thrombogenicity.[87, 93-95]

Although, after restoration of sinus rhythm, electrical reverse remodeling is fast, the LA is in a stunned state and functional recovery is a much slower process.[63, 96, 97] LA remodeling is clinically important as it is related to the

transition of paroxysmal AF to more treatment-resistant AF types such as persistent AF and later chronic persistent AF.[98-100] The extent of atrial remodeling depends on the duration of AF, atrial size and underlying heart disease and is strongly related to the self-perpetuation of AF.[97, 101, 102] The LA functional recovery, following the restoration of the sinus rhythm, depends on the extent of irreversible structural remodeling and is thought to contribute to the development of silent or clinically evident cerebrovascular thromboembolic events, as the majority occur within 10 days after restoration of sinus rhythm. [62, 63, 92, 103-105]

Pathological stimuli such as inflammatory and oxidative stress (DM, obesity and renal failure) as well as volume and pressure overload (HT, left ventricular diastolic and systolic dysfunction and valvular disease) result in an LA structural and functional remodeling promoting AF.[80, 81]

1.4.2 Assessment of left atrial remodeling

Cardiac Imaging

Quantification of the structural remodeling and enlargement of the atria is performed using two-dimensional (2D) echocardiography and cardiac MRI and predefined descriptive norms apply (i.e. normal, mild/moderate/severe enlargement of the left atrium).[106, 107] The LA volume index (LAVI), defined as the LA volume indexed to the body surface area, is universally used for descriptive and predictive purposes.[98-100] Moreover the presence and extent of fibrosis can be assessed by cardiac MRI.[107]

Except for the LA emptying fraction by 2D echocardiography, LA functional assessment is performed using speckle tracking echocardiography and deformation analysis (strain) as well as the corresponding MRI feature tracking analysis.[103, 108, 109] However, definite cut-offs for monitoring LA remodeling, as an indicator of the development and progression of AF, have not been clearly defined.[103]

Electrocardiography

P-wave parameters and indices have descriptively been associated with LA remodeling: P-wave duration (PWD) was independently associated with LA fibrosis and LA mechanical dyssynchrony on cardiac MRI.[110] A prolonged PWD was significantly associated with increased LA size.[111] In another study, of all anatomical parameters, LAVI showed the strongest correlation with both PWD and PR-interval.[112] The P-wave terminal forces in V1 (PwTfV1, the product of the duration of the negative P-wave deflection in V1 and its amplitude) and P-wave dispersion (the difference between the maximum and the minimum PWD in any lead) and the negative P-wave area in lead V1, were associated with LAVI.[113, 114]Atrial electrical remodeling, measured as atrial conduction delay has been positively associated with prolonged PWD.[110, 115]

Although, various studies demonstrated association of PWD, PwTfV1 and P-wave negative area (P(-)area) with the extent of left atrial structural remodeling, electrocardiographic reverse remodeling has been previously described only as a shortening of PWD.[110, 114-117]

1.5 Risk factors for atrial fibrillation

1.5.1 Non-modifiable clinical risk factors

Age

Age is the most important risk factor for AF, with the risk of incident AF doubling with each decade of life. In a European cohort, it has been reported, that the incidence of AF in patients aged 55 to 59 years is 1.1 per 1000 person-years, increasing to 20.7 per 1000 person-years in those > 80 years.[25]

Sex

Women have a 46% lower risk of AF than age-matched men, are more symptomatic from AF, have longer paroxysmal AF episodes and faster ventricular response rates.[38] Women with AF also have a higher risk of stroke and a 2.5-fold higher risk of cardiovascular mortality compared to men.[39, 40]

Ethnicity and genetics

Caucasian ethnicity seems to predispose to AF, supported by the finding that African American ethnicity exhibited a 49% lower risk of incident AF.[41] When genetics were implicated in determining the European ancestry in African Americans, it was found that for every 10% increase in European ancestry there was a 10% increased risk of incident AF.[42] Based on a study on monozygotic twins, the heritability of AF has been estimated to be as high as 62%, indicating a strong genetic component.[118] A number of causative mutations for AF have been identified, specifically the ion channel *KCNQ1*, the cardiac peptide *NPPA*, the transcription factor *TBX5*, and a motor protein *MYL4*.[119]

1.5.2 Modifiable clinical risk factors

Hypertension

HT independently increases the risk of AF by a factor of ≈1.5.[26] A systolic blood pressure of >128 mm Hg and diastolic blood pressure of >80 mm Hg were associated with a 1.5-fold and 1.79-fold higher risk of incident AF, respectively.[27]

Diabetes mellitus

DM is found in 20% of AF population and is associated with a 40% increased risk of AF development as compared to individuals without DM.[28, 29]

Renal insufficiency

A stepwise increase in the adjusted risk of incident AF was observed in patients with renal dysfunction: from HR=1 for patients with glomerular filtration rate (GFR) 60-89 ml/min, to HR=2.03 (1.40 to 2.96) with GFR<30 ml/min.[30]

Obstructive sleep apnea

Diagnosis of OSA and severity are independently associated with incident AF.[31, 120, 121] Central sleep apnea was an independent predictor of incident AF in all adjusted models and was associated with 2- to 3-fold increased odds of developing AF.[31] The prevalence of OSA in patients with persistent AF is 81.6% as compared to 60% in matched individuals without AF.[122]

Obesity

Obesity, measured by the body mass index (BMI) is associated with AF and for one unit increase in BMI there is a corresponding 4% increase in incident AF.[32] Epicardial adipose tissue, correlated with obesity, is highly associated with AF, independently of traditional risk factors.[123, 124]

Heart failure

AF and HF are associated with increased incidence of the other, signifying a bidirectional relationship. AF development is 4-6 times higher in patients with HF and the prevalence of HF was associated with increasing persistence of AF.[26, 33] In addition, patients with combined AF and HF have a worst prognosis and increased mortality. [34]

Life-style related factors

Alcohol consumption of more than three drinks/day resulted in a 34% increased risk of AF.[37] A “dose-response” relationship between alcohol intake and AF revealed a 10% increase in the relative risk of AF for each drink per day beyond the low threshold of only one drink/day.[125] Moderate physical activity, beneficial for AF prevention, is inversely and independently associated with clinical AF incidence and progression.[35, 36]

Risk factors for atrial fibrillation recurrence

Several factors and patient characteristics have been implicated in the risk assessment of AF recurrence. Advanced age, female sex, higher LA diameter, higher LAVI, advanced AF type, duration of AF, the presence of DM or HT,

decreased LVEF, higher BMI are associated with AF recurrence after CV or catheter ablation for paroxysmal or persistent AF. [126-129]

1.5.3 Electrocardiographic predictors

P-wave duration: The PWD with reported cut-offs (125-142ms) is an independent predictor of AF recurrence after CV or PVI; there is a great variation in reported specificities (53-90%) and sensitivities (45.8-78%).[130-137] Additionally, an intermediate prolongation of the PWD (112-119ms) was associated with incident AF with a hazard ratio (HR) 1.22 , (95% Confidence interval (CI): 1.13, 1.31) in the Copenhagen ECG study.[138]

PR-time/interval: A prolonged PR interval was a predictor of AF recurrence after the PVI, HR=1.969, (95%CI: 1.343, 2.886), p=0.001.[139] In the general population, a prolonged PR-interval (≥196 ms for women, ≥204 ms for men) was associated with an increased adjusted risk of incident AF, HR 1.18, (95% CI: 1.06, 1.30) for women and 1.30 (95% CI: 1.17, 1.44) for men.[140] In the Framingham Heart Study, a PR-interval >200 ms was associated with an adjusted HR of 2.06 (95% CI: 1.36, 3.12) for incident AF, compared to individuals whose PR-interval was <200 ms.[141]

P-wave terminal forces in V1 (PwTfV1) and *P-wave frontal axis*: Elevated PwTfV1 (>4000mV·ms) independently predict AF recurrence after PVI with a sensitivity 72.31% and a specificity 74.03%.[142] Moreover, PwTfV1 (>4000mV·ms)[143] and abnormal P-wave axis (<0° or >75°)[144] have previously been associated with incident AF, in the general population.[143, 144] In a meta-analysis, abnormal PTFV1 (>0.04 mm s) was significantly associated with AF occurrence with a pooled OR of 1.39 (95%CI: 1.08, 1.79), $p = 0.01$.[145]

P-wave dispersion (the difference between the maximum and the minimum PWD): The P-wave dispersion, the difference between the maximum and minimum P-wave duration between any lead, with a cut-off ≥ 40 ms was previously associated with AF recurrence with 78% sensitivity and 67% specificity.[130, 146] Additionally, prolonged P-wave dispersion was associated with incident AF.[147]

Electrocardiographic predictors of atrial fibrillation recurrence

ECG characteristics such as increased PWD, increased P-wave dispersion, higher terminal force in lead V1, leftward shift of P-wave axis and increased P-wave area have been associated with AF recurrence after cardioversion or PVI.[130, 131, 148-157]

1.5.4 Biomarkers

Inflammatory factors

Inflammation and its associated immune response are involved in the initiation and maintenance of AF, which, in its turn, promotes inflammation, contributing to atrial remodeling and thrombogenesis, a bidirectional relationship.[158, 159] Inflammatory biomarkers, including CRP and IL-6, were elevated during AF and implicated in outcome prediction.[160-162] Elevated CRP and IL-6 independently predicted thromboembolic complications and stroke in AF patients, indicating a significant role of inflammation in thrombogenicity.[163, 164] Lower CRP and IL-6 prior to CV was associated with reduced risk of recurrence.[165] Oxidative stress and inflammation are central mediators of AF in obesity and diabetes promoting atrial remodeling and leading to the onset and maintenance of AF.[166] P-selectin is involved in the inflammatory response, platelet activation and endothelial activation/injury.[167] P-selectin level have been correlated with blood stasis in the left atrium and elevated levels are observed in AF patients with CHA_2DS_2-Vasc scores ≥ 1 or with LA auricular thrombosis as compared to controls.[168]

Atrial fibrillation and Covid-19

The Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) causing coronavirus disease 2019 (Covid-19), has infected more than 650 million individuals worldwide resulting in 6.7 million deaths as of January 2023.[169] Although Covid-19 primarily affects the respiratory system, it is associated with cardiovascular complications including myocardial damage secondary to acute coronary syndrome or myocarditis, cardiomyopathy, cardiogenic shock, cardiac arrest and arrhythmias.[170] New-onset AF is the most frequent arrhythmia in hospitalized Covid-19 patients, with incidence ranging from 5.4% to 11%, and is associated with poor in-hospital outcomes.[171-175] Patients with new-onset AF reportedly had 2- to 3-fold higher risk of in-hospital all-cause mortality[172, 173, 175], 2-fold increase for major adverse cardiovascular events (MACE), driven mainly by congestive HF and thromboembolic events, prolonged hospitalization and need for intensive care.[171-175]

Moreover, several clinical variables (e.g. advanced age, male sex, increased BMI, history of HF and chronic kidney disease, have been identified as predictors of new-onset AF in hospitalized Covid-19 patients.[172, 175-178] In the light of poor in-hospital outcomes and increased mortality associated with new-onset AF in hospitalized Covid-19 patients, [171-175] early assessment of the risk of new-onset AF is warranted.

Coagululative and fibrinolytic factors

Hypercoagulability in AF is related to the activation of coagulation cascade, platelet activation and impaired fibrinolysis. In patients with acute ischemic

stroke, elevated PTf1+2 was observed in AF patients compared to those without AF.[179] In patients with AF, with or without previous stroke, significantly higher levels of von Willebrand factor, coagulation factor VIII:C, fibrinogen and D-dimer were observed compared to patients without previous stroke and healthy controls.[180] Increased P-selectin, fibrinogen and D-dimer have been identified in chronic AF patients and the use of vitamin K antagonists resulted in normalization of D-dimer levels.[181-183]

Cardiac biomarkers

Cardiac troponin and N-terminal pro b-type natriuretic peptide (NTpro-BNP) are elevated in patients with AF.[184, 185] Elevated levels of these biomarkers were associated with a higher risk of incident AF, AF recurrence after rhythm control intervention and thromboembolism.[185-188] Moreover, NTpro-BNP correlated significantly with the Fazekas score.[189]

Biomarkers of cerebral injury

The presence and extent of brain injury have been associated with elevated S100b, a calcium-binding protein, with good reproducibility.[190-193] Moreover, changes in the levels of S100b may precede radiologically verified cerebral injury.[190, 193, 194] The S100b can be used complementary to brain MRI to detect silent brain injury during catheter ablation of AF. [195] A recent AF ablation study suggested that S100b is released from cardiac glial cells and is a hallmark of acute intra-cardiac neural damage during AF ablation.[196] However this biomarker has not been well studied in the context of CV in AF.

1.6 Clinical management of patients with atrial fibrillation

Clinical management of patients with AF is based on a recently proposed *structured characterization of AF* (the 4S-AF scheme)[197], recommended by the latest (2020) European Society of Cardiology (ESC) guidelines.[19] The 4S-scheme addresses four specific domains in AF: Stroke risk, Symptom severity, Severity of AF burden and Substrate severity.

Stroke risk and prevention

According to the latest (2020) Guidelines for the Management of AF by the European Society of Cardiology, patients with low risk of stroke (CHA_2DS_2-Vasc 0 in males, 1 in females) should not receive OAC and in patients with CHA_2DS_2-Vasc$\geq$2 in males and $\geq$3 in female treatment with OAC is motivated and always recommended.[19] For CHA_2DS_2-Vasc=1 in males and =2 in females, OAC should be considered, especially if age is the contributing risk factor.[19, 198] Simultaneously, the assessment of bleeding risk is necessary; the

HAS-BLED score[199] is currently recommended and any modifiable risk factor should be addressed especially if the total score is ≥3.[19]

Symptom severity

Symptoms and the EHRA symptom score are presented in section 1.3.1.

Severity of AF burden

Symptom control targeting rate or rhythm highly depends on the temporal AF pattern, symptom severity and the total AF burden (total time per monitoring period, number of episodes and the longest AF episode).

In the rate control strategy, the target heart rate of <80 bpm at rest and <110 bpm at moderate exercise can be achieved using beta-receptor blockers, non-dihydropyridine calcium channel blockers, digoxin or amiodarone according to current recommendations or atrioventricular node ablation when pharmacological therapy fails.[19] Rhythm control strategy aims at the restoration and maintenance of sinus rhythm by CV, antiarrhythmic medication or PVI.[19]

While pharmacologic or electrical CV of new-onset or persistent AF is effective in restoring sinus rhythm in the acute setting, the AF recurrence rate at 12 months is high, ranging between 39% and 83%.[200-206] The 12-month success rate of PVI ranges from about 70% to 90% for paroxysmal AF and from 65% to 75% for persistent AF %; however, AF recurrences are still observed on long-term.[207-212] Since PVI targets the AF trigger, compared to CV targeting symptomatology, recent studies have reported that first-line ablation may be more effective in maintaining sinus rhythm in the long term[213], reducing the cumulative effect of multiple AF episodes on irreversible LA structural remodeling.

Substrate severity

Atrial remodeling is characterized by structural, contractile and electrophysiological changes (atrial cardiomyopathy) with relevant clinical manifestations.[214] Assessment of atrial cardiomyopathy, using transthoracic or transesophageal echocardiography, cardiac magnetic resonance and cardiac computed tomography, is crutial in AF management. Major clinical issues in AF, including the prevention of thromboembolic complications and AF progression are influenced by atrial remodeling.[19]

Finally, multidisciplinary management of cardiovascular risk factors and comorbidities, targeting not only lifestyle interventions (weight loss, reduce alcohol intake and regular exercise) but also optimal treatment for HT, HF, coronary artery disease, DM and OSA, are currently recommended.[19]

2. Aims

The overall aim of this thesis was to evaluate and clinically implicate LA remodeling in AF in clinical and rhythm outcomes.

The specific aim were:

Study I

To examine the occurrence and timing of new silent thromboembolic events after CV in anticoagulant-naïve patients with recent onset AF. Secondarily, to explore the effect of short-duration AF and CV on the cognitive function and biomarker of cerebral damage.

Study II

To assess the effects of a short-duration AF episode and CV on thrombogenicity in anticoagulant-naïve patients by analyzing LA hemodynamic and biomarkers reflecting hypercoagulability. Furthermore, to explore the associations of a previous history of AF and the degree of atrial functional recovery.

Study III

To identify novel ECG predictors of AF recurrence suitable for automatic measurements, which compare favorably with current risk factors and to evaluate them in predictive models. A second aim was, to study the reverse atrial electrical remodeling through repeated ECG measures.

Study IV

To evaluate traditional ECG and clinical predictors of new-onset AF, in hospitalized Covid-19 patients, including a novel P-wave index, the Peq-time, the time from P-wave onset to the peak positive P-wave deflection in lead V1. Additionally, to evaluate predictive models of new-onset AF in Covid-19. Secondarily, the impact of new-onset AF on in-hospital clinical outcomes was explored.

3. Methods

3.1 Studies I and II

3.1.1 Study design and population

Studies I and II were conducted on the same population. Patients, without prior anticoagulation, were prospectively recruited after their referral for subacute CV within 48 h after AF onset, from the emergency department, between March 2015 and October 2017. Inclusion and exclusion criteria are presented in Table 4.

Table 4. Inclusion and exclusion criteria in Studies I and II

Inclusion criteria:
1. Age : 18-75
2. Symptom-guided definite AF onset <48 h
3. Eligible for CV within 48 h after symptom debut
Exclusion criteria:
1. Recent (< 3 months) cardioversion of AF or atrial flutter
2. Previous clinical cerebrovascular event
3. Congestive heart failure, NYHA function class III and IV or previously documented moderate or severely decreased LVEF (< 35%)
4. Previously documented moderate or severe valvular disease
5. Intra-atrial thrombus detected with trans-esophageal echocardiography, if performed
6. Atrial flutter, atypical atrial flutter or intra-atrial re-entry tachycardia
7. Contraindications to electrical cardioversion
8. Permanent implanted cardiac device (implantable loop recorders accepted)
9. Ongoing treatment with vitamin K antagonist or direct OAC
10. Contraindication to MRI
11. Known coagulation defects or spontaneous INR or aPTT levels at therapeutic levels
12. Spontaneous conversion to sinus rhythm prior to first MRI

Investigations were scheduled within 2 hours prior to CV, at 1-3 hours after, at 7-10 days after CV and at 30 days after CV (end of study). In **Study I** the serial measurements of brain damage biomarker, serial brain MRI and serial cognitive function tests were analyzed. (Figure 2)
Study II was a predefined sub-study; the serial biomarkers (inflammatory, coagulative and cardiac), the serial echocardiographic examinations and only baseline brain MRI were analyzed. (Figure 2)

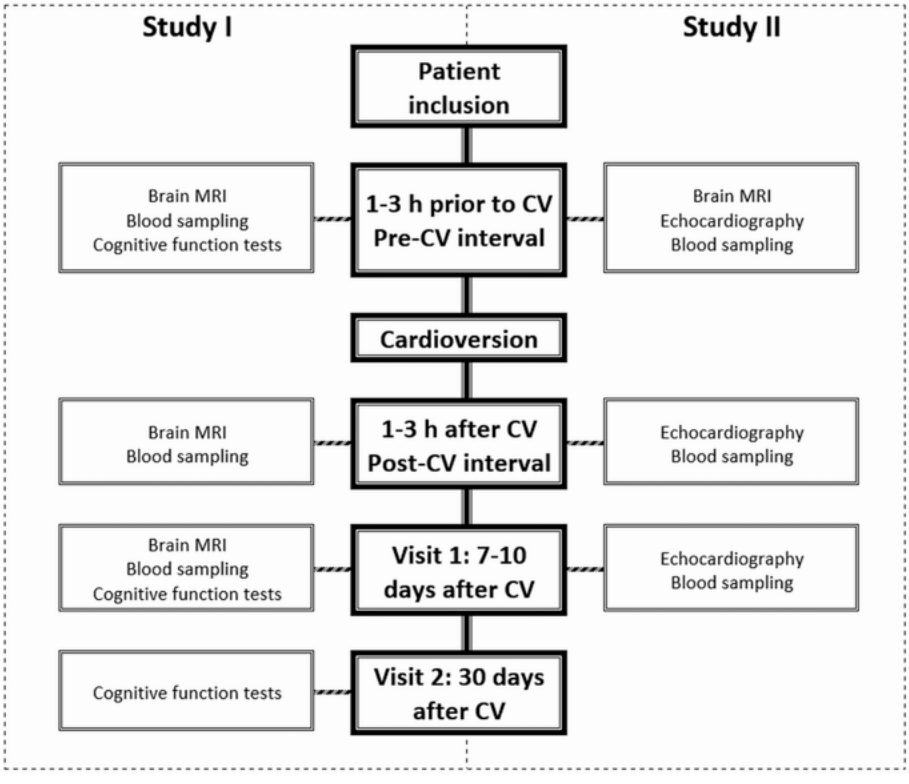

Figure 2. Studies I and II flowchart

The timing of the investigations was related to the dynamic phases of the LA remodeling - reverse remodeling circle. The debut of AF hallmarks the beginning of LA remodeling and loss of contractile function and the period after the restoration of sinus rhythm represents the recovery of the stunned LA, the later associated with the highest thromboembolic event rates after a CV.[62, 215] After CV the patients received a continuous ECG Holter monitor for 7 days. AF recurrence was defined as any AF episode lasting more than 30 s.[216]

3.1.2 Endpoints

The primary endpoint was the occurrence of acute silent thromboembolic events detected on any brain MRI. Secondarily, we explored the associations of short-term AF, CV and clinical characteristics on (i) cognitive function and chronic silent cerebral lesions, (ii) echocardiographically assessed LA function and (iii) cardiac, inflammatory and coagulation biomarkers.

3.1.3 Investigations

Magnetic resonance imaging of the brain

Brain MRIs were done using either a 1.5 Tesla or a 3 Tesla system. The same scanner was used for all three sequential MRI examinations in each patient. The scans were visually evaluated for: (i) the presence, number and size of acute ischemic lesions and (ii) the presence of WMH lesions, old infarcts and incidental findings (baseline MRI scan prior to CV) The WMHs were visually quantified using the Fazekas scale ranging from 0 to 3, where 0 equals normal, 1 to punctate lesions and 3 when extensive and confluent lesions were present.[71]

Echocardiography

Cardiac chamber dimension and function as well as valvular morphology and function were assessed.[106, 217] The LVEF was measured. Focused structural and functional assessment of the LA included: (i) the end-diastolic and end-systolic volumes (LAEDV, LAESV) , (ii) the total emptying fraction (LAEF) and (iii) LA peak longitudinal strain during the reservoir phase (LAεR), the conduit phase (LAεCD) and the contraction phase (LAεCT). The later was assessed using speckle tracking echocardiography for deformation analysis (strain). The LAEDV indexed to body surface area (LAVI) was also calculated.

Cognitive assessment

Trail Making Test A and B (TMT-A, TMT-B) were used to assess cognitive function.[218-220] The TMT-A and TMT-B measure the time (in seconds) needed to complete a specific task. Consequently, shorter times or lower scores indicate better cognitive function. The difference between TMT-A and TMT-B times, considered a measure of cognitive flexibility relatively independent of manual dexterity, was also calculated.[220-222]

Blood sampling and biomarkers

Study I: Biomarker of cerebral injury: protein S100b, a small dimeric 21 kDa calcium-binding protein predominantly expressed by the nervous system.

Study II: Inflammatory biomarkers: interleukin-6 (IL-6), C-reactive protein (CRP) and P-selectin. Cardiac biomarkers: high-sensitivity cardiac troponin T (hs-cTNT) and N-terminal pro-brain natriuretic peptide (NT-proBNP). Coagulation biomarkers: prothrombin fragment 1+2 (PTf1+2), von Willebrand Factor antigen (vWFag), coagulation factor VIII, fibrinogen and D-dimer. Methods for analyzing the biomarkers are presented in Table 5.

Table 5. Biomarker analysis methods

Function	Biomarker	Measurement method	Ref. interval
Study I			
Cerebral injury	**S100b**	Roche® Cobas Elecsys S100b reagent kit.	≤ 0.10 µg/l
Study II			
Inflammation	**CRP**	CRPhs, Roche Diagnostics	<5 mg/L
	IL-6	Quantikine ® HS Human IL-6 Immunoassay, ELISA, R&D Systems	0.495 – 3.92 ng/L
	P-Selectin	Quantikine ®Human P-Selectin/CD62P, ELISA, R&D Systems	0.8 - 50 ng/mL
Cardiac injury and dysfunction	**hs-cTNT**	Elecsys® hs-Troponin T, Roche Diagnostics	<14 ng/L
	NT-proBNP	ARCHITECT i2000 BNP (Abbott, Abbott Park, Illinois)	<330 ng/L
Coagulation	**PTf1+2**	Enzygnost® F 1+2 (monoclonal), Siemens	69 – 229 pmol/L
	vWFag	STA®-Liatest® VWF:Ag, STA-R Max, Stago	0,60 – 1,60 kIE/L
	F-VIII	Asserachrom® VIII:Ag STA-R Max, Stago	0,50 – 1,80 kIE/L
	Fibrinogen	STA®-Fibrinogen 5, STA-R Max, Stago	2,0–4,2 g/L
	D-Dimer	STA®-Liatest® D-Di, STA-R Max, Stago	<900 ng/L

3.1.5 Statistics

The normality of variables was tested using the Shapiro-Wilk test or the one-sample Kolmogorov-Smirnov test. The results were reported as mean ± standard deviation (SD) for normally distributed variables, as median (interquartile range, IQR) for non-normally distributed variables and counts, n and percentage (%) for nominal variables. Normally distributed variables were analyzed

using the student-t test for pairwise comparisons and repeated measures analysis of variance (ANOVA), with the use of Greenhouse-Geisser or Huynh-Feldt correction for violation of Mauchly's test of sphericity for serial results analysis. A value of $p < 0.05$ was set for statistical significance. The data were analyzed using IBM Statistical Package for the Social Sciences, version 25 and 27 for Windows, (IBM Corp. IBM SPSS Statistics for Windows, Armonk, NY, USA).

Study I: The frequencies and associations of categorical variables were assessed using the Pearson χ^2-test. The presence of associations between ordinal variables was analyzed by ordinal regression. The presence of practice effects on cognitive function tests was assessed using the Reliable Change Index (RCI). RCI values bellow 1.96 may denote effect of repetition and values above 1.96 may signalize a change of clinical significance.[223]

Study II: Skewed variables were analyzed using the Wilcoxon signed-rank test for pairwise comparisons, adjusting significance values using the Bonferroni correction for multiple tests and the Friedman's two-way analysis of variance by ranks for serial result analysis. Missing values classified as ''missing at random'' were treated with single imputation.[224] Left-censored data below the lower limit of quantification (LOQ) were treated with simple substitution with LOQ/√2. For the comparative analysis of echocardiographic results, the cohort was divided according to the presence or absence of a history of previous paroxysmal or persistent AF.

Determination of sample size was based on the varying frequencies (4-38 %) of new silent cerebral lesions on brain MRI after various cardiac interventions [225-228]. Based on these observations we argued that a 20 % increase in the incidence of new asymptomatic cerebral ischemic lesions in patients undergoing electrical CV would be clinically meaningful. For a 20% increase in the incidence of silent cerebral lesions following CV, the required number of patients to reject the null-hypothesis with 90% power and at the 0.05 significance level (two-sided) was estimated to be 35.

3.2 Study III

3.2.1 Study design and population

The study population consisted of patients with non-permanent symptomatic AF who had been subject to a rhythm control intervention; either direct CV (CV-cohort) or PVI (PVI-group). The CV-cohort included paroxysmal or persistent AF patients from a retrospective quality registry of subacute (within 48 h) or elective cardioversions conducted during 2015 and May 2016 – March 2017. The PVI-group comprised patients with paroxysmal or persistent AF

included in a prospective randomized clinical trial comparing two cryoballoon techniques for PVI.[209]

The primary hypothesis was that a different P-wave partitioning in V1, namely partitioning by the peak of the positive P wave deflection, would perform superiorly in both the AF recurrence prediction and the RAER analysis compared to the currently used separation into a positive and a negative part by the isoelectric line. The basis of this new concept was that the right and left atrial activation vectors oppose each other in V1 and the peak of the positive deflection marks their equalization. [229, 230]

3.2.2 Endpoints

The primary clinical endpoint was AF recurrence, defined as the presence of AF on a standard 12 leads surface ECG, occurring within 12 months of follow-up, or an AF episode longer than 30 s on 7-day Holter recording (at 6 and 12 months for PVI-group).

3.2.3 Electrocardiographic analysis

The baseline 12-lead ECGs recorded during sinus rhythm after CV (CV-cohort) and prior or after PVI (for patients in AF prior to ablation) were analyzed for P-wave predictors of AF recurrence. The follow-up ECGs, recorded at 6 (±2) and 12 (±2) months after rhythm control intervention, were analyzed regarding the presence of reverse atrial electrical remodeling (RAER). The ECG variables were automatically analyzed and measured from lead V1 using the GE-Marquette 12SL ECG analysis program (GE Healthcare). A detailed description of the variables is shown in Table 6 and illustrated in Figure 3.

3.2.4 Echocardiography

2D echocardiographic examinations were performed within 6 months prior to or 2 months after the baseline visit for the CV-cohort and at baseline for the PVI-group. The LAVI was calculated and used in the predictive analysis.

3.2.5 Clinical variables

Patient characteristics (age, sex, BMI and past medical history) were collected at baseline. Detailed AF history including the duration since the first AF diagnosis, AF type (paroxysmal or persistent), ongoing antiarrhythmic drug at baseline, the number of CVs in the past 12 months and the duration of AF episode prior to intervention (qualitative variable with a cut-off of 48 h) was also collected at baseline.

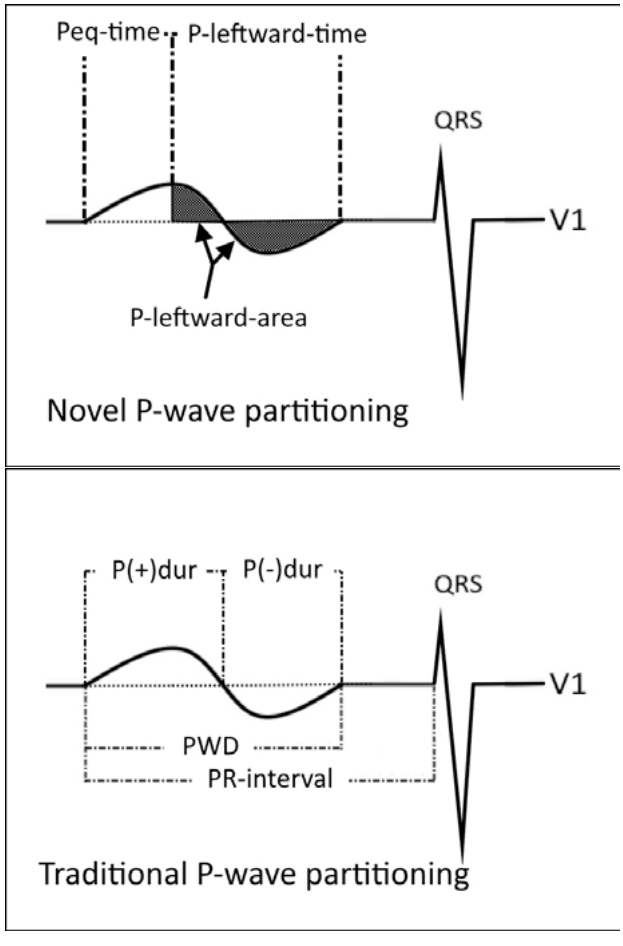

Figure 3. Electrocardiographic variables

Table 6. Electrocardiographic measurements (Study III)

Variable	Definition	Method[a]	Units	Predictive analysis	RAER analysis
P-wave time intervals					
PWD	the total P-wave duration	Auto	*ms*	+	+
P(+)dur	the duration of the positive P wave deflection	Auto	*ms*		+
P(-)dur	the duration of the negative P-wave deflection	Auto	*ms*		+
Peq-time	the time from onset to the peak positive deflection	Auto	*ms*	+	
pP(-)time	the time from onset to the peak negative deflection	Auto	*ms*	+	
Pleftward-time	the time from the peak positive deflection to the offset of P-wave	Calc[b]	*ms*	+	+
PR-interval	the time from the onset of P-wave to the onset of QRS- wave	Auto	*ms*	+	
P-wave amplitudes					
P(+)ampl	the maximum positive amplitude	Auto	*mV*		+
P(-)ampl	the maximum negative amplitude	Auto	*mV*		+
P-wave areas					
P(+)area	the total area under the positive P wave deflection	Auto	*mV·ms*		+
P(-)area	the total area under the negative P wave deflection	Auto	*mV·ms*		+
Pleftward-area	the total area under the P wave deflection corresponding to $P_{leftward\text{-}time}$	Calc[c]	*mV·ms*		+
PwTfV1	the P-wave terminal forces in lead V1, as the product of $P_{(-)ampl} \cdot P_{(-)dur}$	Calc	*mV·ms*	+	+
Other					
Paxis	the frontal plane P-wave axis, analyzed from extremity leads	Auto	degrees	+	
RaLaVBeat	the right and left atrial vector *Beat* time, a novel abstract P-wave time index; it is calculated as the inverse absolute arithmetic difference between the right and left atrial wavelet frequencies; representing wavelength in ms; $RaLaVBeat = \frac{1}{\left\lvert \frac{1}{2 \cdot P_{leftward-time}} - \frac{1}{4 \cdot P_{eq-time}} \right\rvert}$	Calc	*ms*	+	

[a]: Method of measurement; Auto: Automatic measurements, analyzed by GE-Marquette 12SL ECG analysis program; Calc: Calculated using the automatic measurements; RAER: Reverse atrial electrical remodeling; [b]: Pleftward-time = ½· P(+)dur + P(-)dur; c : Pleftward-area = ½· P(+)area + P(-)area;

3.2.6 Statistical analysis

Statistical analysis was performed using SPSS version 28.0.1.0 for Windows. The Shapiro-Wilk test was used to test normality of data. Normally distributed data were reported as mean ± SD and skewed data as median (25^{th}, 75^{th} IQR). Continuous variables were compared between groups using Student's T-test or Mann–Whitney U-test according to normality. Categorical variables were reported as number (percentage) and compared using the Fisher exact test. The Friedman x^2 test was used to analyze the dynamic changes in the repeated ECG measurements. Pearson's correlation coefficient was used to access linear associations between variables. Univariable Cox proportional hazards regression (CoxR) was performed to identify predictors of AF and calculate hazard ratios (HRs). Receiver-operating characteristic curve analysis was used to calculate the optimal cut-off values. Multivariable CoxR was used to analyze adjusted HRs.

Predictive models

Four core predictive models were evaluated for AF recurrence, in order to access the incremental effect of adding electrocardiographic and echocardiographic information:

1. Model ***BC***: included all baseline characteristics (BC) age, sex, BMI, CHA□DS□-VASc score, duration of AF since diagnosis, persistent AF, antiarrhythmic drugs (AAD), treatment group and AF episode duration prior to intervention over 48 h (index AF> 48 h);
2. Model ***iBC-isoECG***: included clinically important baseline characteristics (iBC) that reached the significance level in the univariable CoxR analysis (age, CHA□DS□-VASc, persistent AF, AAD, treatment group and index AF> 48 h) and ECG parameters resulting from partitioning the P-wave by the isoelectric line (*isoECG*: PWD ,P(-)dur, P(+)ampl, P(-)ampl, PR-interval and P(-)area);
3. Model ***iBC-eqECG***: included iBC and ECG parameters resulting from partitioning the P-wave by the peak of positive P-wave deflection (*eqECG*: Peq-time, P-leftward-time, P(+)ampl, P(-)ampl, PR-interval time and Pleftward-area,);
4. Model ***iBC-novel***: included iBC and the two novel predictors, Peq-time and RaLaVBeat.

All models were analyzed with and without LAVI as a covariate using both binary logistic regression and machine learning methods, using Multilayer Perceptron (MLP) analysis, thus totally eight models in each analysis. MPL is a feed forward neural network, consisting of three layers: i) an input layer, ii) a binary output layer performing classification and prediction and iii) a number of hidden layers, the computational engine of MLP. The neurons in the

MLP were trained using a supervised learning technique called back-propagation and the database was randomly partitioned into a training subset (approximately 70%) and a testing subset (approximately 30%).
The performance of the predictive models was comparatively assessed using the following metrics: recall (sensitivity), specificity, accuracy, precision (positive predictive value), F1-score, support and area under ROC curve, derived from the training subset confusion matrix. [231, 232]

3.3 Study IV

3.3.1 Study design and population

Study IV was a predefined sub-study of an international cohort study including the University of Washington (UW) Medical Center (Seattle, WA), the Karolinska Institute University (Stockholm, Sweden), the Uppsala University (Uppsala, Sweden), and the Copenhagen University (Copenhagen, Denmark).[233-235]

The design of the original study was reported previously.[233] In short, adult patients, hospitalized for Covid-19 diagnosis (ICD-10-CM U07.1), confirmed by polymerase chain reaction, with a digitally stored ECG at admission were eligible for inclusion. Patients with history of AF were excluded from the sub-study. The duration of hospitalization in Covid-19 care unit, including of the time in ICU, was considered the study's follow-up. Data were collected from electronic medical records between March 2, 2020, and February 28, 2021. Standard 12-lead ECGs at admission and the most recent ECG within one year prior to admission were digitally stored.

3.3.2 Endpoints

The primary endpoint was the occurrence of new-onset AF at admission or during the hospital stay in a Covid-19 unit or ICU, documented in the patient's medical records (verified by telemetry or standard 12-lead ECG). Secondarily, we explored new-onset AF associations with clinical outcomes, as described below, including all-cause mortality, major adverse cardiovascular events (MACE: cardiogenic shock, heart failure, new-onset AF, ventricular arrhythmias, cardiac arrest, acute coronary syndrome and thromboembolic events), as well as discharge characteristics.

3.3.3 Predictors of new-onset atrial fibrillation

Electrocardiographic variables

All digital ECG files were imported and automatically re-analyzed using the GE-Marquette 12SL ECG analysis program (GE Healthcare). The ECG automatic analysis included the QRS duration in V1, the QRS-wave frontal plane axis, the P-wave frontal axis and the following P-wave variables from lead V1 (Table 7):

Table 7. P-wave variables (Study IV)

Variable	Definition	Units
PWD	P-wave duration: the time from the P-wave onset to the P-wave offset of	ms
P(-)dur	Negative P-wave deflection duration: the time from the onset of negative P-wave deflection to the P-wave offset	ms
Peq-time	Time to peak positive P-wave: the time from the P-wave onset to the maximum positive P-wave deflection	ms
pP(-)time	Time to peak negative P-wave: the time from the P-wave onset to the maximum negative P-wave deflection	ms
PR-interval	PR interval: the time from the P-wave onset to the onset of the QRS complex	ms
P(-)ampl	The negative P-wave amplitude: the maximum negative P-wave deflection amplitude	mV
P(-)area	The area of the negative P-wave deflection : the area above the negative deflection to the isoelectric line	mV·ms

Additionally, the P-wave terminal forces in lead V1 (**PwTfV1**), as the product of P(-)ampl x P(-)dur, was calculated. The most recent ECG (within 1 year) was used for analysis in patients with new-onset AF at admission.

Clinical variables

Demographics (e.g. age, sex and BMI) and pre-existing co-morbidities (e.g. HT, coronary artery disease, chronic lung disease and any cardiomyopathy) were considered in the predictive analysis for new-onset AF. Moreover, initial admission to the ICU and the level of respiratory support and the length of stay (LOS) in ICU and Covid-19 care unit were also evaluated. Finally, laboratory parameters included the peak levels of C-reactive protein (CRP), N-terminal pro-brain natriuretic peptide (NT-proBNP), Troponin-T (Tn-T) and D-dimer, were also considered in the predictive analysis.

3.3.4 Statistical analysis

Statistical analysis was performed using SPSS version 28.0.1.0 for Windows (IBM Corporation, Armonk, New York). The Shapiro-Wilk test was used to

test normality of data. Normally distributed data were reported as mean (±SD) and skewed data as median (25th, 75th IQR). Continuous variables were compared between groups using Student's T-test or the Mann–Whitney U-test according to normality. Categorical variables were reported as counts (percentage) and compared using the Fisher exact test (or Fisher-Freeman-Halton for >2 groups). Logistic regression was used to analyze and calculate of odds ratios (ORs) and confidence intervals (CIs). The receiver operating characteristic (ROC) analysis was used to evaluate predictor performance and calculate the recommended cut-off values for the ECG variables. Simple imputation for missing values was applied for BMI only to allow adequate inclusion in predictive models (missing at random: 12.9%).

Predictive models

Four predictive models of new-onset AF were evaluated using multivariable logistic regression analysis and internally validated with bootstrapping (N=1000 samples):

1. Model **BC-CoMorb** included basic demographic characteristics (age, sex, BMI) and the presence of pre-existing comorbidities (hypertension, chronic lung disease, coronary artery disease and cardiomyopathy);
1. Model **BC-ICU-PWD$_{115ms}$** included the PWD ≥115ms, age, sex, BMI and ICU referral at admission;
2. Model **BC-ICU-PR$_{190ms}$** included the PR-interval ≥ 190ms and the same clinical variables as in the 2nd model;
3. Model **BC-ICU-Peq-time$_{33ms}$**: included the Peq-time ≥33ms and the same clinical variables as in the 2nd model.

Predictive models were comparatively evaluated using the following performance metrics: specificity, sensitivity, the area under the ROC curve, accuracy and balanced accuracy (weighted average of sensitivity and specificity, correcting accuracy for the imbalance in outcome classes).[231, 232, 236, 237]

4. Results

4.1 Studies I and II

4.1.1 Population and outcomes

Forty-three patients were included in studies I and II. A history of paroxysmal AF was present in 17 (39.5%) patients and persistent AF in 9 (20%), leaving 17 (39.5%) with first-onset AF. Basic demographic characteristics are presented in Table 8.

Table 8. Basic characteristics of the population in studies I and II

Characteristics	**Patients n = 43**
Sex, females, n (%)	7 (16.3)
Age, years	55±9.6
BMI, kg/m^2	26±3.4
Hypertension, n (%)	9 (20.9)
Diabetes mellitus, n (%)	2 (4.7)
Vascular disease, n (%)	1 (2.3)
AF duration from symptom onset to diagnosis (hours)	13.3±11.7
Previous history of paroxysmal or persistent AF, n (%)	26 (60)
CHA_2DS_2-VASc = 0, n (%)	21 (48.8)
CHA_2DS_2-VASc = 1, n (%)	19 (44.2)
CHA_2DS_2-VASc ≥ 2, n (%)	3 (6.9)
Plasma creatinine, µmol/L	82.8±13.5
Systolic blood pressure (mmHg)	125±13
Diastolic blood pressure (mmHg)	81±9
ACE/ARB medication, n (%)	8(18.6)
Antiplatelet therapy, n (%)	0(0)
Beta receptor blockers, n (%)	9(20.9)
Heart rate at presentation (bpm)	110±31

Forty-one patients were successfully electrically cardioverted and two patients converted spontaneously to sinus rhythm after the first brain MRI examinition. Eight of the 43 (18.6%) patients received treatment with novel oral anticoagulants after CV; seven male patients prior to discharge (four patients with

CHA_2DS_2-VASc score≥2 and three patients aged > 65 year) and one patient on the 6th day due to peripheral emboli. Holter monitoring after CV detected AF recurrence in 4 (9.3%) patients; 3 had a paroxysmal AF episode (33 and 183 s) and one patient had persistent AF.

4.1.2 Brain imaging, biomarkers of brain injury and cognitive function (Study I)

Magnetic resonance imaging

Radiological signs of recent acute ischemic lesions corresponding to micro-emboli were not detected on the baseline MRI prior to CV, or on the MRI examination after CV, immediately or at 7-10 days. However, WMH lesions were identified at baseline in 21/43 (49%) patients. Visual quantification based on the Fazekas score was 0 in 22 (51%) patients, 1 in 18 (42%) patients and 2 in 3 (7%) patients.

By partitioning the study population into four major groups according to the extent of WMH (Fazekas score 0 or ≥ 1) and the presence or absence of thromboembolic (TE) risk factors (CHA_2DS_2-VASc score 0 or ≧ 1), the TE risk as defined by CHA_2DS_2-VASc score ≥ 1, was significantly associated with a higher incidence of WMH, Pearson $\chi^2(1,N=43)=3.95$, p=0.047. (Figure 4).

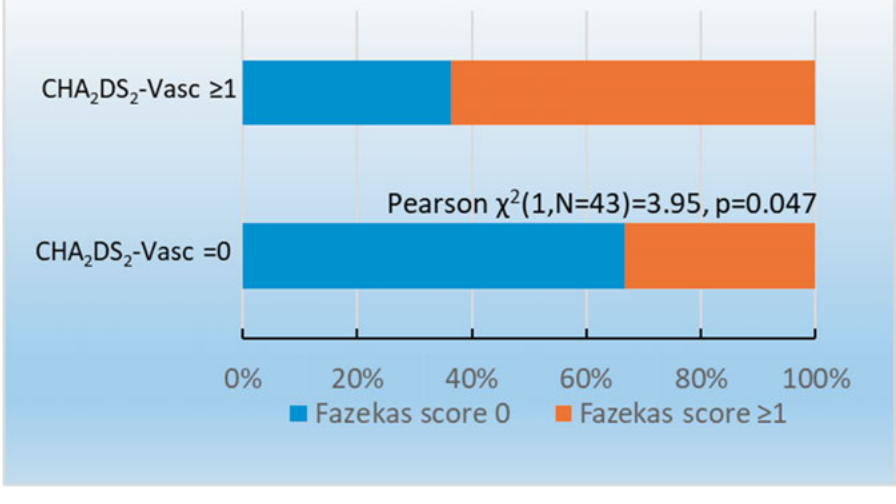

Figure 4. Association between the CHA2DS2-Vasc score and the Fazekas score

Brain injury biomarker

All measurements of S100b were within the normal reference interval. The baseline S100b (0.0472 ±0.0182) µg/l increased after CV (0.0551 ±0.0185) µg/l and then decreased 7-10 days after CV (0.0450 ±0.0186) µg/l. Both

changes were statistically significant. Additionally, in repeated measure analysis, the overall directional change was statistically significant, $F(2,68)=12.22$, <0.001.

A non-significant trend for higher levels of S100b in patients with a CHA_2DS_2-VASc score ≥1 was observed compared to patients without TE risk.

Cognitive function

All TMT-A and TMT-B scores fell within the normal age-stratified reference range.[219] The TMT-A, TMT-B and ΔTMT times improved (decreased) with time and a statistically significant overall improvement was found for all three tests. The TMT-B and ΔTMT at 30 days were significantly better as compared to the preceding tests at 7-10 days. Additionally, this improvement of was not attributed to test repetition as indicated by the Reliable Change Index (RCI) of 2.67 and 3.0 respectively. Previous history of persistent AF was associated with statistically significant prolonged test times in TMT-B prior to CV and TMT-A and TMT-B at 30 days after CV (Table 9).

Table 9. Cognitive function and previous history of persistent AF

	Test (sec)	History of persistent AF		One-way ANOVA	
		No (n=34)	Yes (n=9)	F(1,41) =	p value
Prior to CV	**TMT-A**	22.1±7.9	27.8±8.8	3.44	0.071
	TMT-B	48.7±22.6	68.0±29.9	4.48	**0.04**
	ΔTMT	26.0±18.5	40.2±26.1	3.22	0.08
7-10 days after CV	**TMT-A**	20.9±10.1	26.0±9.9	1.79	0.188
	TMT-B	46.7±28.2	64.1±35.8	2.41	0.128
	ΔTMT	25.7±20.4	38.1±27.4	2.25	0.141
30 days after CV	**TMT-A**	19.3±4.2	24.8±7.3	8.56	**0.006**
	TMT-B	38.7±12.3	52.9±26.1	5.54	**0.023**
	ΔTMT	19.5±11.6	28.1±22.5	2.55	0.118

Finally, a trend for prolonged test times for TMT A and B was observed in patients with white matter hyperintensities.

4.1.3 Echocardiographic findings and Biomarkers (Study II)

Echocardiography

Baseline LAVI was normal in all patients. A statistically significant overall improvement of LAEF in repeated measure analysis was observed. The overall increase in all three LA deformation indices (LAεR, LAεCD and LAεCT) was also statistically significant. (Table 10). Moreover, when comparing LA peak longitudinal strain at 1-3 h after CV versus 7-10 days after restoration of sinus rhythm, there was a statistically significant increase of LAεR, $p<0.001$, LAεCD, $p=0.009$, and LAεCT, $p=0.023$.

Table 10. Echocardiographic results: repeated measure ANOVA

Echocardiographic parameter	Prior to CV	After CV	7-10 days after CV	Repeated measure ANOVA	p value
LAVI (ml/m^2)	31.3±9.4	32.3±9,3	31.8±10.9	F(1.89 , 76.4)=0.29	0.722
LAEDV (ml)	62.4±20.6	67.0±19.9	64.9±22.1	F(2 , 84)=1.34	0.267
LAESV (ml)	38.9±13.9	34.9±14.2	31.1±13.3	F(2 , 84)=10.47	**<0.001**
LAEF (%)	37.3±12.5	48.7±9.7	52.7±9.2	F(1.83 , 76.8)=30.75	**<0.001**
LAεR (%)	11.9±7.0	20.5±5.2	25.6±6.8	F(2 , 84)=56.99	**<0.001**
LAεCD (%)	7.7±5.0	11.4±3.2	13.2±4.0	F(1.73 , 72.75)=23.63	**<0.001**
LAεCT (%)	N/A	9.0±3.3	12.1±4.5	t(42)=−2.4	**0.023**
E/A ratio	N/A	1.3±0.3	1.2±0.4	t(42)=1.51	0.138
LVEDV (ml)	87.4±21.2	112.2±16.4	117.5±21.2	F(2 , 84)=55.97	**<0.001**
LVESV (ml)	39.2±11.2	49.3±12.6	46.3±10.6	F(2 , 84)=13.55	**<0.001**
LVEF (%)	55.9±8.4	56.2±7.4	60.5±6.4	F(1.79 , 75.11)=7.76	**0.001**

Although LAEF normalized at 7-10 days, it was significantly lower in patients with versus those without a prior AF history, 50.3±8.8% versus 56.3±8.7%, p=0.032. (Figure 5)

Biomarkers

The inflammation and endothelial dysfunction biomarkers, IL-6 and P-selectin showed a statistically significant overall decrease in the serial measurement analysis from prior to CV to the 7-10 days after CV. The CRP did not change significantly. Both cardiac biomarkers, hs-cTNT and NTpro-BNP, decreased statistically significantly, after CV. The biomarkers of coagulation, PTf1+2 and fibrinogen, decreased statistically significantly in the serial analysis from prior to CV to the 7-10 days after CV. The vWfAg increased transiently after CV and decreased 7-10 days after CV, showing an overall statistically significant change in serial analysis. The FVIII and D-Dimer did not change significantly (Table 11). Patients with WMH tended to have of higher CRP, hs-cTNT, NTpro-BNP, and PTf1+2 than patients without WMH, though the difference did not reach statistical significance.

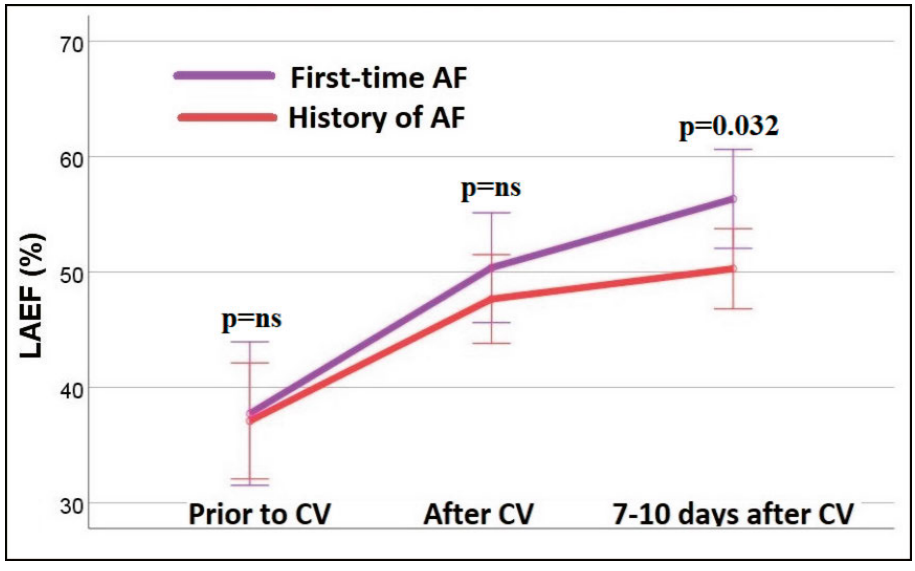

Figure 5. LAEF in patients with and without AF history

Table 11. Biomarker tests; pairwise comparison and serial measurements analysis

	Biomarker (Ref. units)	Prior to CV	Post CV	Prior vs Post CV		7-10 days after CV	Post CV vs 7-10 days		Overall change	
				Z score[#]	p value[§]		Z score[#]	p value[§]	χ^2 (2) [##]	p value
Inflammatory	**CRP <5 mg/L)**	1.0 (0.71-2.86)	1.0 (0.71-2.28)	-1.57	0.3	1.5 (0.71-3.0)	-0.83	0.8	3.22	0.2
	IL-6 (0.495 – 3.92 ng/L)	2.3 (0.95-2.48)	2.0 (1.1-2.72)	-0.86	1	1.7 (0.63-1.97)	3.82	**<0.001**	16.22	**<0.001**
	P-Selectin (0.8 – 50 ng/mL)	36.7 (27.9-44.2)	34.3 (24.4-38.9)	2.31	0.061	34.9 (29.2-38.4)	0.53	1	9.27	**0.01**
Cardiac	**hs-cTNT (<14 ng/L)**	6.0 (5.0-9.0)	6.0 (3.5-8.0)	3.72	**0.001**	5.1 (3.5-7.9)	1.46	0.4	32.46	**<0.001**
	NT pro-BNP (<330 ng/L)	1200 (827-1750)	882 (534-1360)	3,56	**0.001**	86 (45-135)	4.85	**<0.001**	71.30	**<0.001**
Coagulation	**PTf1+2 (69 – 229 pmol/L)**	194 (134-204)	169 (113-199)	2.59	**0.029**	161 (110-185)	0.48	1	10.98	**0.004**
	vWfAg (0.60 – 1.60 kIE/L)	1.23 (0.99-1.7)	1.36 (0.99-1.64)	0.97	0.9	1.23 (0.9-1.42)	1.45	0.44	6.25	**0.044**
	FVIII (0.50 – 1.80 kIE/L)	1.44 (1.16-1.96)	1.44 (1.04-1.85)	-1.73	0.08	1.38 (1.03-1.8)	-0.89	0.6	3.28	0.19
	Fibrinogen (2–4.2 g/L)*	3.50 (3.15-4.37)	3.45 (3.07-4.05)	1.98	0.1	3.30 (3.17-4.45)	0.28	1	6.84	**0.033**
	D-Dimer (<900 ng/L)*	469 (275-993)	409 (249-1326)	-0.97	0.3	456 (281-1109)	0.59	0.5	2.71	0.25

4.2 Study III

4.2.1 Population and outcomes

Study population

368 patients were included in the study (CV-cohort: n=230, PVI-group: n=138). Patients' characteristics at baseline are listed in Table 12.

Table 12. Patient characteristics (CV-cohort and PVI group)

Characteristic	***CV-Cohort***	***PVI-Cohort***
	n=230 (62.5%)	n=138 (37.5%)
Age, years	68 [64-72]	63 [55-68]
Female sex, n (%)	57 (24.8%)	37 (26.8%)
Body mass index, kg/m^2	27.0 [24.6-30.1]	27.1 [25.2-30.3]
Past history:		
Hypertension, n (%)	161 (24.8%)	74 (53.6%)
Diabetes mellitus, n (%)	29 (12.6%)	13 (9.4%)
Heart failure, n (%)	38 (16.5%)	12 (8.7%)
Severe valvular disease, n (%)	4 (1.7%)	1 (0.7%)
Stroke[a], n (%)	16 (7%)	6 (4.3%)
Vascular disease, n (%)	36 (15.7%)	9 (6.5%)
Renal disease[b], n (%)	17 (7.4%)	0 (0)
COPD, n (%)	6 (2.6%)	7 (5.1%)
CHA□DS□-VASc score	2 [1-3]	1 [1-2]
AF history		
Duration since 1st diagnosis, years	4 [0.57-9]	4.6 [2.2-9.3]
Persistent AF, n (%)	207 (90%)	77 (55.8%)
Antiarrhythmic at baseline, n (%)	67 (29.1%)	85 (61.6%)
Previous CV/s, 12 months, n (%)	162 (70.4%)	103 (74.6%)
Index AF duration > 48 hours, n (%)	144 (62%)	29 (21%)
Echocardiography	61 (26%)	127 (92%)
LAVI	40 [35.5-47.2]	38.5 [32-47.22]
Electrocardiography		
Baseline, n (%)	230 (100%)	138 (100%)
6 months follow-up, n (%)	111 (48%)	135 (97.8%)
12 months follow-up, n (%)	93 (40%)	131 (94.9%)

Outcomes

AF recurred in 175 (76.1%) patients in the CV-cohort and 39 (28.3%) patients in the PVI-group; in total 214 (58.2%) patients during the 12 months follow-up. (Table 13)

Table 13. Patients characteristics: comparing outcome groups

Characteristic	***No AF recurrence***	***AF recurrence***	***p-value***
	n=154	n=214	
Age, years	64 [58-70]	67 [63-71]	**0.001**
Female, n (%)	36 (23.4%)	58 (27.1%)	0.419
Body mass index, kg/m^2	27.1[25.2-30.3]	27.1[25.7-30.1]	0.973
Past history:			
Hypertension, n (%)	88 (57.1%)	147 (68.7%)	**0.023**
Diabetes Mellitus, n (%)	20 (13%)	22 (10.3)	0.421
Heart failure, n (%)	15 (9.7%)	35 (16.4%)	0.068
Severe valvular disease, n (%)	4 (2.6%)	1 (0.5%)	0.082
Stroke[a], n (%)	3 (3.9)	16 (7.5%)	0.153
Vascular disease, n (%)	15 (9.7%)	30 (14%)	0.217
Renal disease, n (%)	8 (5.2%)	9 (4.2%)	0.656
COPD, n (%)	8 (5.2%)	5 (2.3%)	0.143
CHA□DS□-VASc score	2[1-2]	2[1-3]	**<0.001**
AF history			
Duration since 1st diagnosis	4.1[1.8-10]	4[1-9]	0.331
Persistent AF, n (%)	95 (61.7%)	189 (88.3%)	**<0.001**
Antiarrhythmic at baseline, n (%)	75 (48.7%)	77 (36%)	0.018
Index AF >48 hours, n (%)	54 (35%)	119 (55%)	**<0.001**
Previous CV, 12 months, n (%)	113 (73.4%)	152 (71%)	0.621
PVI	99 (46.3%)	39 (25.3%)	**<0.001**
Echocardiography	97 (62.9%)	91 (42.5%)	
LAVI	36.9 [31.6, 44.7]	42 [36, 49.2]	**0.003**
Electrocardiography			
Baseline, n (%)	154 (100%)	214 (100%)	
6 months follow-up, n (%)	113 (73.3)	133 (62%)	
12 months follow-up, n (%)	109 (70%)	115 (53%)	

4.2.2 Electrocardiographic changes for measuring reverse atrial electrical remodeling

In the non-recurrent AF group (AF(-)group) the PWD decreased significantly, from 114 [100,124] ms at baseline to 108 [79,120] ms at 6 months and 106 [78,123] ms at 12 months, $x^2(2)= 54.77$, $p<0.001$, in contrast, such decrease was not seen in the recurrent AF group (AF(+) group). Compared with AF(-) group, the PWD was significantly prolonged in the AF(+) group at 6 and 12 months but not at baseline,. The P(+)dur increased significantly whereas P(-)dur decreased significantly during follow-up, but only in the AF(-) group. The P(+)dur was significantly longer in the AF(+) group at baseline and the P(-)dur was significantly longer in the AF(+) group at 12 months compared to the AF(-) group.

The novel Peq-time did not change significantly with time and was the only part of the P-wave in V1 that was static. It was significantly longer in the AF(+) versus the AF(-) group both at baseline (30 [24,28] ms versus 28 [20,33] ms, p=0.001) and at 6 months (32 [26,38] ms versus 30 [24,35.5] ms, p=0.027). Conversely, the P-leftward-time decreased significantly during follow-up in the AF(-) group and was significantly longer in the AF(+) versus the AF(-) group at 12 months, 83 [46, 98] ms versus 72 [43, 86] ms , p=0.012.

The PR-interval decreased significantly in both the AF(-) and AF(+) group during follow-up and was significantly longer at baseline, 6 and 12 months in the AF(+) group versus the AF(-) group. The absolute PwTfV1 decreased significantly during follow-up in both patient groups. The absolute PwTfV1 was significantly lower in the AF(-) versus the AF(+) group at 12 months. The absolute P(-)area decreased significantly in both groups during follow-up. The absolute P(-)area was significantly lower in the AF(-) group at 6 and 12 months, as compared to the AF(+) group.

Comparatively to the P(-)area and PwTfV1, the novel P-leftward-area showed the largest overall change over time for both groups in the study population, $x^2(2)= 52.15$, $p<0.001$.

The RaLaVBeat was significantly higher in the AF(+) versus AF(-) group at baseline alone, 290.6 [154.9, 644.8] versus 213 [118.3, 433.2] ms, p=0.008.

A significant positive correlation was found between baseline Peq-time and LAVI, $r(184)=0.158$, $p=0.032$. The ratio of Peq-time/P-leftward-time was also positively correlated to LAVI, $r(183)=0.166$, $p=0.023$. The Peq-time was significantly longer in patient with persistent AF as compared with patients with par-AF, 30 [22, 36] versus 28 [20, 34] ms, p=0.037 at baseline, 32 [26, 38] versus 30 [24, 34] ms, p=0.028 at 6 months and 32 [25, 38] versus 28 [20, 34] ms , p=0.035 at 12 months after the intervention.

4.2.3 Clinical, electrocardiographic risk factors and predictive models for atrial fibrillation recurrence

Clinical characteristics

Univariable Cox-regression analysis revealed advanced age, persistent AF, HT, HF, high CHA□DS□-VASc score, increased LAVI, use of AAD at baseline, PVI treatment and duration of index AF > 48 h, were associated with significantly higher risk of AF recurrence. Only persistent AF and PVI were identified as independent predictors of AF recurrence in the multivariable analysis (Table 13).

Conventional ECG predictors

A prolonged PR-interval was associated with a significantly higher risk os AF recurrence as opposed to measures of PWD, PwTfV1, pP(-)time and P-axis, on univariable CoxR analysis. Although the PwTfV1 was statistically significant in the multivariable CoxR analysis, it was higher in the AF(-) group as compared to AF(+) group and the ROC curve analysis yielded a non-significant association AUC=0.533, p=0.278, (95%CI: 0.473-0.593). (Table 13).

Novel ECG predictors

In multivariable CoxR, prolongation of the novel Peq-time was associated with higher risk of AF recurrence with an adjusted HR of 1.020, (95% CI:1.009-1.031), for each 1 ms increase, p<0.001. According to ROC curve analysis the Peq-time cut-off for predicting AF recurrence was 33 ms (sensitivity 44.6% , specificity 75.2%, AUC=0.601, p=0.001, 95% CI: 0.542-0.659) with an adjusted HR 1.809, (95% CI: 1.358-2.412), p<0.001 (Table 13).

Prolonged RaLaVBeat, a novel P-wave time index, was associated with a significantly higher risk of AF recurrence on multivariable CoxR analysis with an adjusted HR of 1.006 (95% CI: 1.002-1.011), p=0.006 for each 50 ms increase. The $RaLaV_{Beat}$ cut-off for predicting AF recurrence was 521ms as obtained by the ROC curve analysis (sensitivity 33.3%, specificity 81.3%, AUC=0.572, p=0.022, 95% CI: 0.510-0.633) with an adjusted HR of 1.589, (95% CI:1.185-2.131), p=0.002 (Table 14).

Table 14. Predictors of AF recurrence

	Univariable analysis		*Multivariable analysis*	
Variable	***HR (95% CI)***	***P value***	***HR (95% CI)***	***P value***
Clinical Characteristics				
Age	1.029 (1.001-1.047)	**0.001**	1.000 (0.983-1.017)	0.990
BMI	1.004 (0.973-1.036)	0.807	-	-
Gender	1.127 (0.834-1.524)	0.436	-	-
Time since 1st AF	0.989 (0.969-1.009)	0.277	-	-
Persistent AF	3.317 (2.183-5.039)	**<0.001**	1.862 (1.190-2.914)	**0.006**
HT	1.347 (1.009-1.799)	**0.042**	1.034 (0.768-1.393)	0.826
HF	1.562 (1.087-2.244)	**0.015**	1.145 (0.787-1.666)	0.480
Stroke	1.239 (0.960-1.599)	0.097	-	-
DM	0.849 (0.546-1.319)	0.466	-	-
Vascular disease	1.340 (0.910-1.072)	0.137	-	-
CHA□DS□-VASc sc.	1.254 (1.122-1.401)	**<0.001**	1.052 (0.926-1.194)	0.439
COPD	0.551 (0.227-1.337)	0.181	-	-
Renal disease	0.836 (0.429-1.631)	0.600	-	-
Valvular disease	0.276 (0.039-1.969)	0.169	-	-
LAVI	1.015 (1.002-1.028)	**0.027**	1.011 (0.996-1.025)	0.125
AAD	0.692 (0.523-0.915)	**0.009**	1.126 (0.839-1.513)	0.454
PVI	0.201 (0.142-0.285)	**<0.001**	0.247 (0.164-0.372)	**<0.001**
Index AF > 48 h	2.099 (0.601, 2.752)	**<0.001**	1.160 (0.864-1.557)	0.322
Conventional P-wave indices				
PR_{time}	1.008 (1.005-1.012)	**<0.001**	1.003 (0.999-1.007)	0.103
P_{dur}	1.001 (0.995-1.007)	0.836	0.998 (0.992-1.004)	0.470
PwTfV1	1.000 (0.999-1.008)	0.071	1.006 (1.002-1.010)	**0.006**
P_{axis}	1.001 (0.996-1.006)	0.559	0.999 (0.994-1.004)	0.600
$pP_{(-)time}$	0.999 (0.994-1.003)	0.531	0.996 (0.992-1.001)	0.099
Novel P-wave indices				
$P_{eq\text{-}time}$	1.017 (1.006-1.027)	**0.002**	1.020 (1.009-1.031)	**<0.001**
$P_{eq\text{-}time}$ >33 ms	1.728 (1.301-2.294)	**<0.001**	1.796 (1.346-2.396)	**<0.001**
$RaLaV_{Beat}$	1.002 (0.998-1.006)	0.346	1.006 (1.002-1.011)	**0.006**
$RaLaV_{Beat}$>521ms	1.679 (1.256-2.244)	**<0.001**	1.581 (1.178-2.121)	**0.002**

The incremental effect on AF-free survival when the Peq-time was trichotomized according to 25th and 75th quartiles is shown in Figure 6.

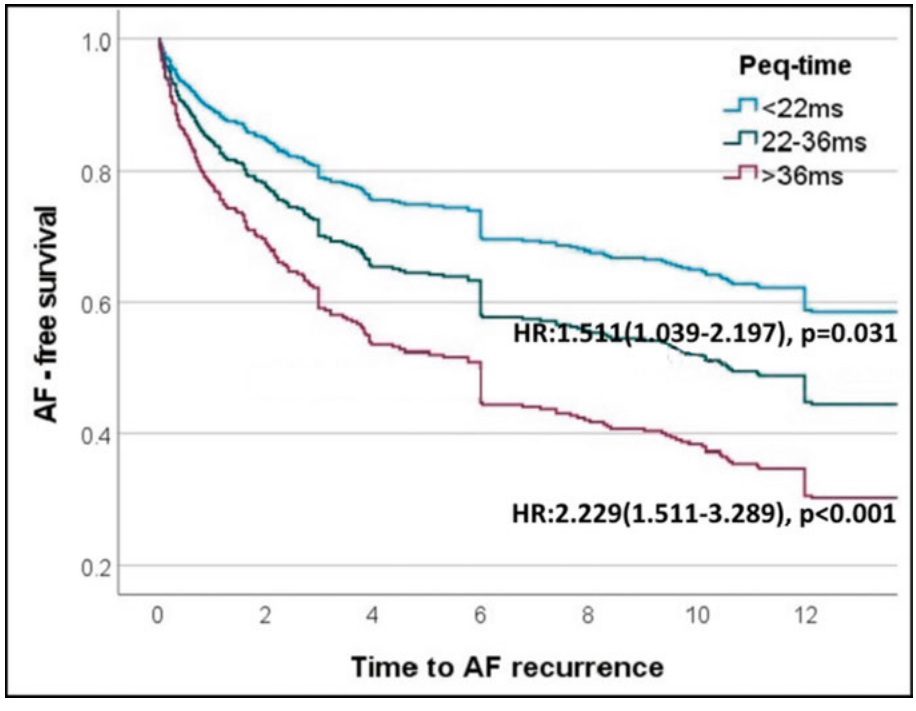

Figure 6. Kaplan-Meier arrhythmia-free survival curves for Peq-time

Machine learning and logistic regression predictive models

All MLP models were superior to logistic regression models in predicting AF recurrence. The addition of either ECG or echocardiographic variables, or both, improved model performance. The AUC of the 16 models is comparatively illustrated in Figure 7.

The machine learning model MLP-iBC-eqECG-LAVI that included age, CHA_2DS_2-VASc score, AF type, antiarrhythmic treatment , type of intervention, the duration of AF episode prior to intervention (>48 h), the LAVI, Peq-time, P-leftward-time, P(+)ampl, P(-)ampl, PR-interval and P-leftward-area, had the highest AUC=0.923, sensitivity (87.5%) and specificity (92.5%). The ROC curves of the four MLP models including LAVI as a covariate are jointly plotted in Figure 8.

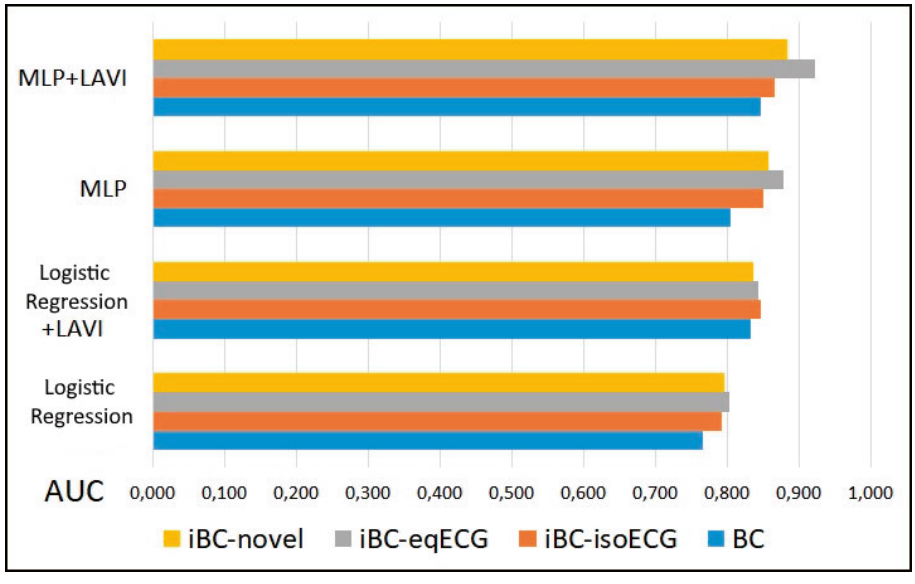

Figure 7. Performance of all predictive models

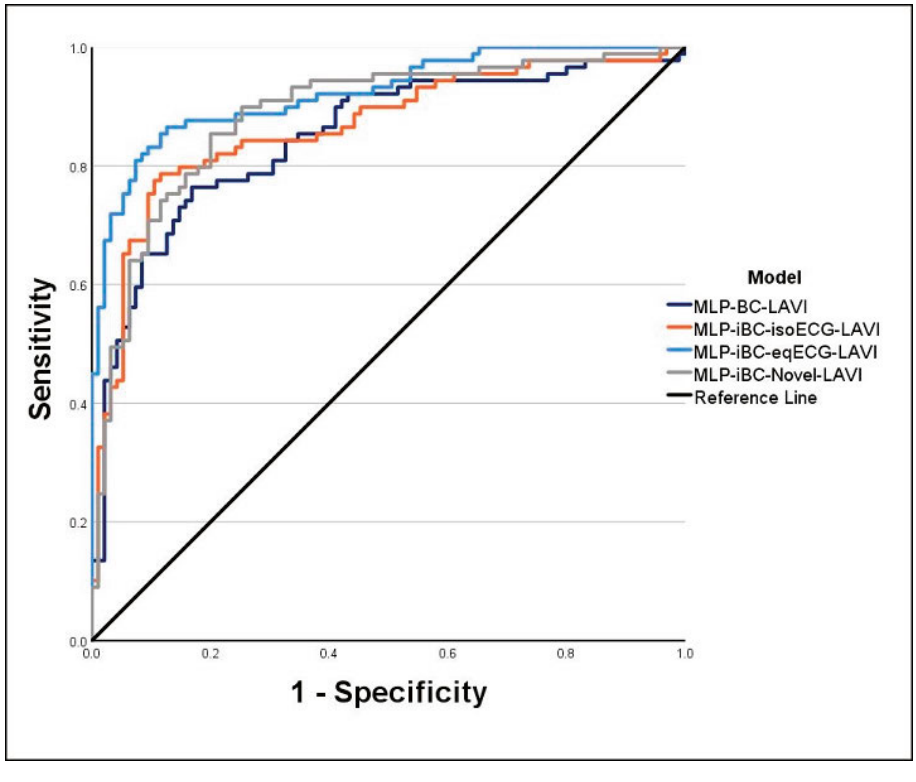

Figure 8. ROC curves of the four MLP models including LAVI

4.3 Study IV

4.3.1 Population and outcome

A total of 921 patients were included. New-onset AF was documented in 59 (6.4%) patients, of whom 15 (25.8%) presented with AF at admission and 44 (74.2%) developed AF later. The incidence of new-onset AF varied between 4% and 7.1% across the four participating universities, but the differences were not statistically significant.

Patients with new-onset AF were significantly older, were more likely male and more frequently suffered from pre-existing coronary artery disease, as compared to those without new-onset AF. Initial admission to the ICU and use of respiratory support were significantly more frequent in patients with new-onset AF than those without (Table 15).

Table 15. Population characteristics at admission

Characteristic	***Overall*** n=921	***Without AF*** n=862 (93.6)	***New onset AF*** n=59 (6.4)	***p value***
Demographics				
Age, years	60.9 (±16.2)	60.5 (±16.2)	67.5 (±15.4)	**0.001**
Body mass index, kg/m2	28.5 (±6.5)	28.4 (±6.0)	29.5 (±6.7)	0.210
Female sex, n (%)	357 (38.8)	343 (39.8)	14 (23.7)	**0.018**
Enrolling site				0.620
Karolinska Institutet, n (%)	345 (37.5)	322 (93.3)	23 (6.7)	
Univ. of Copenhagen, n (%)	150 (16.3)	144 (96)	6 (4)	
Uppsala University, n (%)	253 (27.5)	235 (92.9)	18 (7.1)	
Univ. of Washington, n (%)	173 (18.8)	161 (93.1)	12 (6.9)	
Comorbidities				
Hypertension, n (%)	451 (49)	417 (48.4)	34 (57.6)	0.180
Chronic Lung Disease, n (%)	127 (12.7)	117 (13.6)	10 (16.9)	0.438
Coronary artery disease, n (%)	101 (11)	89 (10.3)	12 (20.3)	**0.028**
Cardiomyopathy, n (%)	223 (24.2)	211 (24.5)	12 (20.3)	0.533
Admission characteristics				
Initial admission in ICU, n (%)	260 (28.2)	221 (25.6)	39 (66.1)	**<0.001**
Any respiratory support, n (%)	286 (31.1)	248 (28.8)	38 (64.4)	**<0.001**
NIPP ventilation, n (%)	119 (12.9)	112 (13.0)	7 (5.9)	
Intubation, n (%)	156 (16.9)	127 (14.7)	29 (49.2)	
ECMO, n (%)	11 (1.2)	9 (1.0)	2 (3.4)	

NIPP: Non-invasive positive pressure; ECMO: Extracorporeal membrane oxygenation

4.3.2 Clinical, electrocardiographic risk factors and predictive models for new-onset atrial fibrillation in Covid-19

ECG predictors of new-onset atrial fibrillation

The Peq-time (24±16 ms versus 20±12 ms, p=0.021) and the PR-interval (170±42ms versus 155±24 ms, p=0.009), were significantly longer in new-onset AF patients versus those without, in contrast, PWD, PwTfV1, P(-)area, P-axis and pP(-)time were not significantly lower. Prolonged Peq-time and PR-interval were independent ECG predictors of new-onset AF, both when treated as continuous or categorical variables with respective cut-off. After adjustment for age, sex and BMI, the Peq-time >33ms had an OR of 2.81 (95%CI: 1.53, 5.17), p<0.001, and the PR-interval>190ms an OR of 4.33 (95%CI: 1.98, 9.47), p<0.001. Additionally, the PWD of >115 ms independently predicted new-onset AF, OR 1.99 (95%CI: 1.15, 3.46), p=0.014.

Clinical predictors

Advanced age, male sex and increased BMI were independent predictors of new-onset AF; for every decade increase in age the OR was 1.33, (95%CI: 1.11, 1.60), p=0.002; for male patients the OR was 2.32, (95%CI: 1.24, 4.35), p=0.009 and for every 5 units increase in BMI the OR was 1.31, (95%CI: 1.06, 1.62), p=0.012.

Initial admission to the ICU and the use of any respiratory support were associated with significantly increased odds for new-onset AF; OR 7.67, (95%CI: 4.09, 14.42), p<0.001 and OR 4.14, (95%CI: 2.33, 7.38), p<0.001, respectively. Moreover, an extended stay by one week in the ICU or in the Covid-19 care unit increased the odds of new-onset AF, OR 1.52, (95%CI: 1.27, 1.82), p<0.001 and OR 1.15, (95%CI: 1.06, 1.24), p=0.001, respectively.

Predictive models

Comparing the four predictive models showed that the BC-ICU-Peq-time$_{33ms}$ model and the BC-ICU-PR$_{190ms}$ models exhibited the highest balanced accuracy, 79.7% and 79.4% and highest AUC 0.824 and 0.826, respectively (Figure 9).

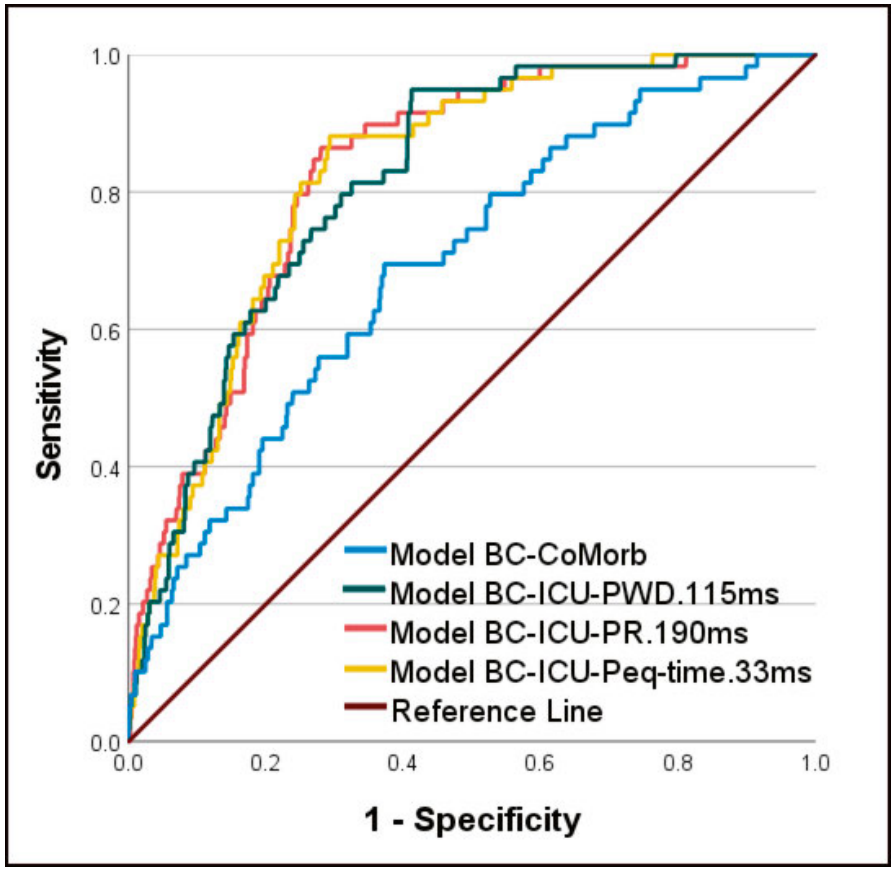

Figure 9. ROC curves for the four predictive models

Of the remaining two models, the BC-ICU-PWD_{115ms} model was superior to the BC-CoMorb model with balanced accuracy 76.8% versus 66.1% and AUC 0.817 versus 0.691, respectively. Of the three models that included ECG parameters, the BC-ICU-$Peq\text{-}time_{33ms}$ and BC-ICU-PR_{190ms} models exhibited the highest specificities (74.8% and 70.7% respectively), as compared to BC-ICU-PWD_{115ms} model with specificity of 58.8%.

From calibration standpoint, all logistic regression models were well calibrated in the lower segment of predicted probability (0–20%), which necessitated adjustment of the classification cut-off value. Internal validation of the logistic regression models using bootstrapping (N=1000) did not alter the results.

Clinical outcomes associated with new-onset atrial fibrillation

The all-cause mortality rate was higher in patients with new-onset AF than those without (40.7% versus 13%, $p<0.001$). The presence of new-onset AF

was associated with a significantly higher OR for in-hospital mortality, unadjusted OR 4.59, (95%CI: 2.63, 8.01), and adjusted for age, sex and BMI, OR 3.31, (95%CI: 1.79, 6.13), p<0.001 (Figure 10).

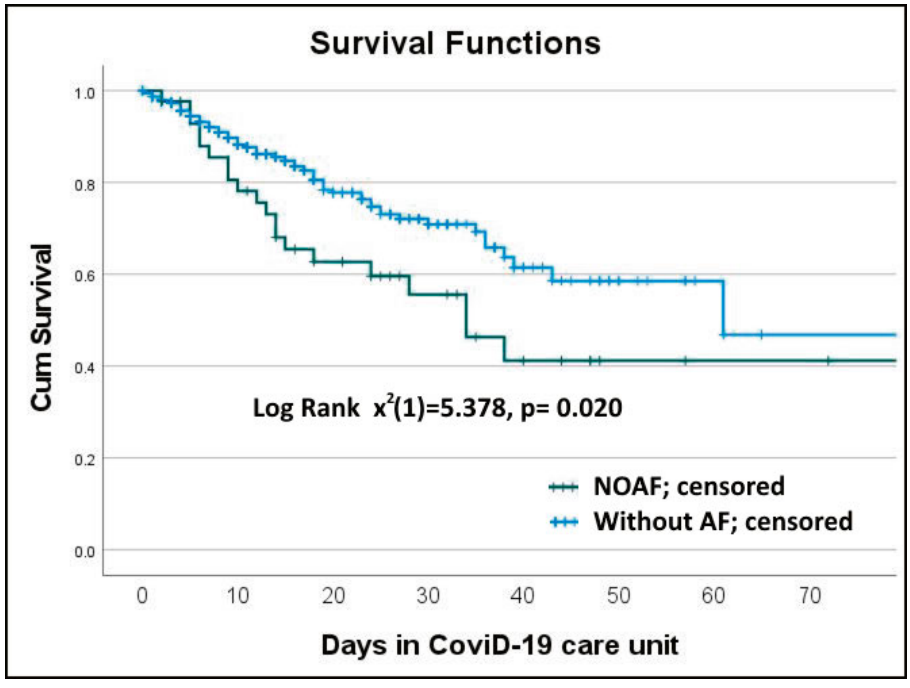

Figure 10. Survival plots for patients with and without new-onset AF

Patients with new-onset AF had a higher incidence of a MACE, 40.7% versus 14% in patients without, p<0.001; mainly driven by heart failure, 27.1% versus 3.7%, p<0.001 and thromboembolism, 18.6% versus 9.4%, p=0.039. The length of stay in ICU and Covid-19 care units was significantly longer in patients with new-onset AF versus in those without. Moreover, the peak levels of CRP, NT-proBNP, Tn-T and D-dimer were significantly higher in patients with new-onset AF than those without. Among the survivors, 27.1% of the new-onset AF patients were discharged to a non-Covid-19 unit for continued care, versus 14.7% without new-onset AF, p=0.016.

5. Discussion

Atrial remodeling is characterized by structural, contractile and electrophysiological changes (atrial cardiomyopathy), clinically manifested as AF.[214] Prevention of thromboembolic complications and AF progression, major issues in the clinical management of AF, are influenced by atrial remodeling.[19] The mechanism of thrombogenesis is multifactorial, as previously described in the Virchow triad, [238, 239] atrial enlargement and contractile dysfunction and an enhanced thrombogenic milieu, contribute synergically to the development of overt and silent, acute and chronic cerebral lesions.[63, 76, 103]

5.1 Brain imaging, biomarkers of brain injury and cognitive function (Study I)

Brain magnetic resonance imaging

Cerebral diffusion weighted MRI is a highly sensitive method.[225, 240, 241] However, in our cohort of OAC-naive patients, cardioverted within 48 h, no signs of acute silent cerebral lesions were detected. Hence our primary hypothesis was not substantiated in any of the three MRI, covering the three time intervals with the highest risk of TE post CV: from AF onset to CV, immediately after CV, and 7-10 days after CV during recovery of the left atrial contractile function. To our knowledge, this was the first prospective study investigating the incidence and timing of clinically silent cerebral lesions with repeated brain MRI in OAC-naïve patients with recent onset AF cardioverted within < 48 h after AF onset.

It was reported that silent cerebral embolism were detected 4 weeks after CV in 4.7% of 127 persistent AF patients with OAC for at least 4 weeks prior and 4 weeks after trans-esophageal echocardiography guided CV.[242] On the contrary, in a series of 62 patients with persistent AF, CHA_2DS_2-Vasc score 1.8±1.4 and at least 4 weeks effective OAC prior to elective CV, new silent brain lesions were not detected prior or 24-h after CV[69]. In a similar series of 50 persistent AF patients with OAC and CHA_2DS_2-Vasc score 2.7±0.7, MRI at baseline and 14-days after elective CV showed no new cerebral lesions[243]. Patients in both of these trials had higher CHA_2DS_2-Vasc scores as compared

to the patients in Study I. The initiation of OAC after CV in 8/43 (18.6%) patients in Study I, may have contributed to the absence of silent TE events.

In a large, retrospective Swedish study, the risk of clinically overt thromboembolic complications was higher in patients without versus those with OAC at 30 days following electrical CV of recent onset AF (<48 h), OR 2.54 (95% CI: 1.70, 3.79), after adjustment for CHA_2DS_2-Vasc score factors.[244] In the retrospective FinCV study, including 2,481 AF patients, cardioverted within 48 h and without OAC prior or after CV, the incidence of clinically evident TE events after CV was only 0.7%, within 30 days.[105] The risk of TE events, however, increased significantly from 0.4% in patients with CHA_2DS_2-Vasc score < 2 to 2.3% in those with scores ≥5, none of whom were on OAC.[105] Moreover, if the delay from AF onset to CV exceeded 12 hours the risk of TE events increased from 0.3% (<12 h) to 1.1% (24-48 h) emphasizing the importance of early rhythm treatment in patients without prior anticoagulation.[105, 245]

Given the low CHA_2DS_2-Vasc score in Study I, the incidence of chronic WMH was unexpectedly high (49%), as compared to the previously reported prevalence of 39.8% in the general population.[246] We also observed a significant association between the CHA_2DS_2-Vasc score and the presence of WMH. Although WMH are often considered sequelae of infection or inflammation in patients younger than 50-60 years, there is growing evidence of a clear association between AF and WMH.[68] In another study, WMH were observed in 56.4% of persistent AF patients prior to CV and 67.6% of paroxysmal AF patients prior to PVI. [69, 70] Another study reported that the CHA_2DS_2-Vasc score was an independent predictor for the presence of WMH and the Fazekas score was positively correlated with the CHA_2DS_2-Vasc scores [65], which supports our findings of an association between CHA_2DS_2-Vasc score and the degree of WMH.

Biomarker for brain damage

The finding of a significant increase in circulating levels of S100b after CV in Study I, should be interpreted with caution. The use of S100b has been associated with good reproducibility for predicting the presence, timing and extent of brain damage.[190-194] Elevated levels of S100b were associated with acute asymptomatic brain injury during catheter ablation of AF suggesting increased sensitivity and a complementary tool to brain MRI.[195] A recent AF ablation study suggested that S100b is released from cardiac glial cells and is a hallmark of acute intra-cardiac neural damage during AF ablation.[196] However, whether the same mechanism could explain the rise in S100b after CV is, however, unclear.

Changes in S100b levels may also be secondary to extra-cerebral sources (adipose tissue, myocardium, intrinsic cardiac nervous system, skeletal muscle) [196, 247], use of propofol for sedation during CV[248, 249], stress[250, 251] and renal

insufficiency.[252] Consequently, to what extent the transient increase of S100b after CV and restoration of sinus rhythm may indicate minor cerebral damage not detected by MRI is unclear.

Cognitive function

The trail making tests A and B tests improved at the three sequential time intervals. Both tests are sensitive to practice effects, however the RCI values indicated that the observed changes were indeed clinically significant meaningful and gave no support for such practice effects.[253]

The cognitive decline observed in AF has been attributed to stroke and silent cerebral infarcts, and treatment with OAK has been associated with reduced risk of dementia.[254] The assumption of silent ischemic lesions undetectable by MRI, could not explain the late onset of improvement in cognitive function. Even though transient cerebral hypo-perfusion, mental stress during AF episodes and the gradual recovery of the LA contractile function are potential explanations of this improvement, these changes should be interpreted with caution, given that all TMT scores were normal. In support of such a mechanistic explanation is, however, the observation of longer TMT-A and TMT-B times in patients with a previous history of persistent AF versus those with paroxysmal AF or recent onset AF history, which is further consistent with another study showing an association between cognitive decline and AF progression[255].

5.2 Echocardiography and Biomarkers (Study II)

Echocardiography

When sinus rhythm was restored after CV, LA mechanical stunning was evident by the decreased LAEF, which normalized within 10 days and represents one element of Virchow's triad. Despite the significant LA functional recovery and LAEF normalization at 7-10 days post-CV, LAEF was still significantly lower in patients with a history of paroxysmal or persistent AF compared with those with new-onset AF. Irreversible structural remodeling after previous episodes of AF (progression of disease) and slower functional reverse remodeling, could be a possible explanation. Previously, a lower LAEF was associated with disease severity (persistent or permanent AF versus paroxysmal AF) and increased LAVI.[256] Moreover, LAEF seem to be significantly lower in persistent AF patients with arrhythmia recurrences after LA ablation versus those without, indicating that more extensive irreversible remodeling is an arrhythmia precursor.[257]

The presence of irreversible remodeling and fibrosis, identified during electro-anatomical mapping as low-voltage zones, have been associated with decreased LAEF, LAεR, LAεCD, and LAεCT in paroxysmal AF patients.[258]

Moreover, extensive LA fibrosis on cardiac MRI, was inversely associated with LA emptying fraction, longitudinal strain during reservoir, conduit and contractile phases.[259] In Study II, the LA peak longitudinal strain during the reservoir and conduit phase prior to CV were lower in patients with a previous AF history as compared to those without. Although LAεR, LAεCD and LAεCT improved significantly, they did not normalize in both patient groups at 7-10 days. LA deformation indices are strongly associated with LA fibrosis and AF progression, and as decreased indices are observed in patients with cryptogenic stroke, these early signs of LA remodeling, may be used to identify or predict a thrombogenic milieu.[258-261]

Biomarkers

In Study II we observed a significant overall decrease of IL-6, P-selectin, hs-cTNT, NTpro-BNP, PTf1+2, and fibrinogen, and a significant transient increase of vWfAg, from the time while in AF to the time of reverse remodeling after restoration of sinus rhythm is consistent with previous reports.[159, 239] Elevated levels of IL-6 and CRP, have been previously associated with AF severity, AF recurrence after CV and catheter ablation, as well as risk of stroke.[159, 239] Elevated CRP and IL-6 levels have previously been associated with increased LA size and long lasting AF episodes indicating an association to LA structural changes and remodeling.[162, 262] Higher troponin levels and elevated NTpro-BNP have been associated with incident AF, with AF recurrence after CV, and with thromboembolic risk. [185, 186, 188, 263-265] A hypercoagulability state in AF, as was reflected by elevated PTf1+2, fibrinogen and vWfAg in Study II, has previously been reported even during the first 24 hours of paroxysmal AF.[266-270] Indcluding only OAC-naïve patients, in Study II, eliminated interactions related to the coagulative system.

Moreover, in patients with WMH, we noted a non-significant trend for higher CRP, hs-cTNT, NTpro-BNP and PTf1+2 values. Although CRP and PTf1+2 have been linked to the presence and severity of WMH in older adults, and hs-cTNT and fibrinogen with the presence of WMH in patients with acute ischemic stroke, little is known about their relation to WMH in the AF population without stroke.[271-277] Since AF is associated not only to the presence of WMH, but also to the activation of inflammatory and coagulation systems, the findings in Study II further supports the perception that AF is a marker of a cardiovascular disease, linking AF and WMH, beyond thromboembolism.[68, 70, 278, 279]

5.3 Electrocardiographic changes for measuring reverse atrial electrical remodeling (Study III)

Using the novel partitioning, the initial part of the P-wave, the Peq-time, remained static during follow-up and was significantly prolonged not only in the AF(+) group but also in patients with persistent AF. The remaining part (the dynamic part) expressed as P-leftward-area showed the strongest variance in repeated measures analysis, as compared with PwTfV1, P(-)area and PWD, in describing electrocardiographically RAER. By contrast, the currently used separation of the P-wave by the isoelectric line results in two time periods, P(+)dur and P(-)dur, that changed significantly but in opposite directions during follow-up. Thus, the dynamic decrease of the PwTfV1 (the product of P(-)ampl x P(-)dur), may overestimate RAER, since these changes are counteracted be the increase in the P(+)dur. The morphological changes of the P-wave in lead V1 are illustrated in Figure 11.

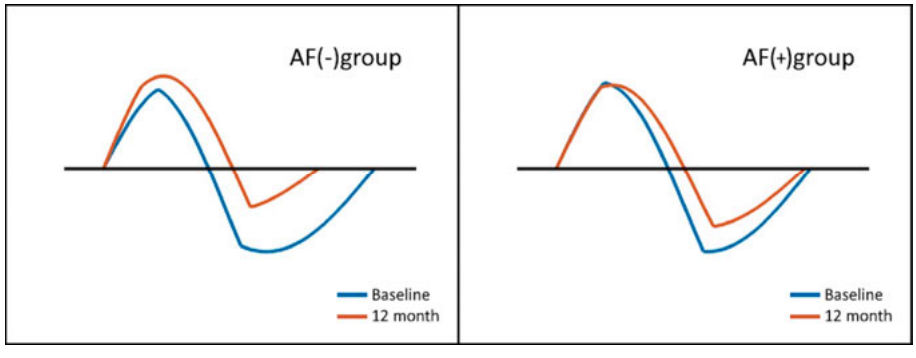

Figure 11. P-wave morphological changes during follow-up

In previous studies, atrial remodeling measured as atrial conduction delay or atrial fibrosis, was positively associated with prolonged PWD. [110, 115] The observed significant shortening of PWD, in Study III, reflects the electrocardiographic reverse remodeling in the atria following the intervention. Although, various studies demonstrated association of PWD, PwTfV1 and P(-)area with the extent of LA structural remodeling, electrocardiographic reverse remodeling have been previously described only as a shortening of PWD.[110, 114-117]

5.4 Predicting atrial fibrillation recurrence (Study III)

Electrocardiographic predictors

The PWD, with cut-off values between 120-150 ms, has been used in several studies for predicting AF recurrence after rhythm control interventions.[280] We introduced a novel P-wave index for prediction, the Peq-time in V1, which,

with the cut-off 33ms, more accurately predicted AF recurrence than the PWD, as indicated by the similar PWD values at baseline in the recurrent and non-recurrent groups. Although the breakthrough of LA depolarization cannot be assessed with precision using surface ECG, the directional differentiation of right and LA activation vectors may be assessed in lead V1, where they oppose each other and the peak of the positive deflection marks their equalization.[229, 230] The Peq-time signifies the initial right atrial activation, the inter-atrial conduction and the initial left intra-atrial conduction and activation, which may explain its predictive value as a marker of disease progression, as indicated by its significant prolongation in persistent AF versus paroxysmal AF patients. In Study III, the Peq-time for predicting of AF recurrence outperformed both the PwTfV1 and the P(-)area, both of which were previously reported as significant predictors of AF recurrence in non-permanent AF patients.[145] Another novel AF predictor introduced in Study III, was the RaLaVBeat, which outperformed both the PWD, PwTfV1 and the P(-)area. The RaLaVBeat had a lower sensitivity and higher specificity than Peq-time.

The difference between the maximum and minimum PWD between any lead (P-wave dispersion), with cut-off ≥ 40 ms was previously associated with AF recurrence with 78% sensitivity, 67% specificity.[130, 146] The Peq-time, the primary finding of Study III, showed lower sensitivity (44%) but higher specificity (75%), as compared to P-wave dispersion. Because, according to the Study III protocol, only automated ECG measurements were included, the P-wave dispersion was, by default, not included in the predictive analysis.

Undoubtedly, an increased LAVI is, up to date, the best predictor of AF recurrence post CV and PVI, with a reported sensitivity of >80% and specificity of >90%, which is superior to other predictors including PWD and PwTfV1.[281, 282] Assessment of LAVI requires echocardiographic examinations which, apart from higher costs, is time-consuming and skill-intensive.[282, 283]

Predictive models

Neural networks have been shown to offer greater flexibility and yield better results, especially if the prediction accuracy is of paramount concern in classifying a dichotomous dependent variable. This may not only explain our observation that all MLP models derived from the novel partitioning of P-wave performed superiorly, but also that MLP models were superior to the corresponding logistic regression models. [231, 232] The observation of the higher predictive performance of MLP models in Study III, with the highest AUC=0.923, combining basic characteristics, atrial specific echocardiographic and ECG parameters, may be explained by use of atrial specific ECG indices. Machine learning models using patient characteristics combined with cardiac imaging variables for prediction of AF recurrence after PVI reported AUCs between 0.700 and 0.766. [284-286] Deep neural networks trained on electrograms or ECG signals improved the prediction accuracy of AF recurrence

after PVI when combined with clinical features, reporting an AUC= 0.731.[287] Other machine learning models combining heart rate variability and clinical features could successfully predict AF recurrence after PVI with an AUC=0.850.[288]

To our knowledge, Study III was the first to use a different partitioning of the P-wave in V1 for identifying novel variables for AF recurrences prediction and description of atrial reverse remodeling.

5.5 Predicting new-onset atrial fibrillation in Covid-19 (Study IV)

Electrocardiographic predictors

The novel Peq-time, outperformed both PwTfV1 and P-wave axis in predicting new-onset AF patients and patients with Peq-time > 33ms had almost three times higher odds to develop new-onset AF than those with Peq-time < 33ms. In the general population, abnormal PwTfV1 (<-4000mV·ms)[143] and abnormal P-wave axis (<0° or >75°)[144] have previously been associated with incident AF, but such measures failed to predict new-onset AF in Study IV. In the general population, a prolonged PR interval (≥196 ms for women, ≥204 ms for men) was associated with an increased adjusted risk of incident AF, HR 1.18, (95% CI: 1.06, 1.30) for women and 1.30 (95% CI: 1.17, 1.44 for men.[140] In the Framingham Heart Study, a PR-interval >200 ms was associated with an adjusted HR of 2.06 (95% CI: 1.36, 3.12) for incident AF, as compared with individuals whose PR-interval was <200 ms.[141] A lower cut-off value, in study IV, a PR-interval >190ms, was associated with a more than four times higher risk of new-onset AF as compared with patients with PR-interval <190ms.

In the general population, an intermediate prolongation of the PWD (112-119ms) was associated with incident AF with a HR 1.22, (95% CI: 1.13, 1.31) in the Copenhagen ECG study.[138] Moreover, a prolonged PWD was also reported to be an independent predictor of new-onset AF in patients with HF and HT.[289, 290] These results are in alignment with Study IV; hospitalized Covid-19 patient with PWD>115ms had an almost double risk of new-onset AF as compared with those with PWD<115ms.

Clinical predictors

Male sex[175, 177] and advanced age[175, 178, 291, 292] have previously been associated with increased risk of new-onset AF in Covid-19 patients, which was confirmed in Study IV. We found that for every 5 units increase in BMI there was a 31% higher risk of new-onset AF. These results are in line with the observation that the adjusted HR for AF or atrial flutter per unit of increase in BMI,

was 1.08, 95% CI (1.05, 1.11) in men and 1.06 95% CI(1.03, 1.09) in women, in the general population.[293]

Pre-existing comorbidities such as HT, cardiomyopathy, chronic lung disease or coronary artery disease were not significantly associated with new-onset AF in Study IV. These results are in line with some previous reports[173, 177, 294, 295], while in other observational studies HT[178, 291, 292], cardiomyopathy[178, 291], coronary artery disease[291, 292], chronic lung disease[291, 294], chronic kidney disease[291, 292, 294] were found to be associated with new-onset AF in hospitalized Covid-19 patients. These conflicting results may, in part, be explained by the fact that the exaggerated inflammatory response, cytokine storm and tissue hypoxia observed not only in Covid-19, but also in other viral pneumonias and associated with the disease severity, play an important role in the development of new-onset AF, along with pre-existing comorbidities.[170, 296-299]

We observed that measures of the severity of Covid-19 such as initial admission to the ICU and the need for respiratory support, increased the odds of new-onset AF by over 7.5 and 4 times respectively. Our results are in line with previous studies reporting that admission to ICU [172-174, 178, 291], prolonged stay[295] in the ICU or in the Covid-19 unit[172, 291, 292], and need for respiratory support[172, 173, 177, 295] were associated with higher risk of new-onset AF during hospitalization. Moreover, elevated inflammatory biomarkers such as CRP[172, 173, 178, 291], acute phase response biomarkers such as D-dimer[172, 291, 292] and cardiac biomarkers such as troponin[291] and NT-proBNP[172, 173, 291] were also associated with the development of new-onset AF during hospitalization, results confirmed in Study IV as well.

Predictive models

Four predictive models were examined, one based on demographics and pre-existing comorbidities and three models tailored for Covid-19 based on demographics, disease severity and ECG measures. The latter, BC-ICU-Peq-time$_{33,}$ BC-ICU-PR$_{190ms}$ and BC-ICU-PWD$_{115ms}$ predictive models had higher balanced accuracy, than the BC-CoMorb model, due to the combination of atrial specific ECG predictors and Covid-19 severity.

The predictive importance of disease severity for new-onset AF was reported in a previous study of patients with sepsis; in a nomogram model which included age, international normalized ratio, fibrinogen, C-reaction protein, sequential organ failure assessment score, HF, and dopamine use, an AUC of 0.845, , (95% CI: 0.804, 0.886) in its external validation was reported.[300] Because pre-existing comorbidities were not independently associated with new-onset AF, the predictive performance of the BC-CoMorb model was expectedly lower in Study IV. These result are in accordance with previous data demonstrating that Covid-19 had the highest association with incident AF, OR 3.12, (95%CI: 2.61, 3.710), as compared to HF 1.72, (95%CI: 1.50, 1.96),

coronary artery disease OR 1.43, (95%CI: 1.27, 1.60) and valvular disease OR 1.42, (95%CI: 1.26, 1.60) in the general population.[301]

Atrial fibrillation related clinical outcomes in Covid-19

In agreement with previous studies, patients in Study IV with new-onset AF had over three times higher risk of all-cause mortality than those without.[175, 176, 291] Furthermore, new-onset AF was previously associated with a higher incidence of major cardiovascular adverse events[170, 174, 292, 295, 296], results that were confirmed in Study IV. Undoubtedly, risk stratification of patients with Covid-19 for new-onset AF risk could potentially improve prognosis.

To our knowledge Study IV was the first study identifying independent ECG predictors of new-onset AF in hospitalized adult Covid-19 patients. Since prolonged Peq-time, PWD and PR-interval reflect an already diseased (remodeled) atria, even in the absence of AF, the importance of inflammatory and oxidative stress on a vulnerable substrate should be emphasized in the development of new-onset AF.

6. Limitations

Studies I and II were based on a small prospective cohort which may limit and underestimate the true incidence of silent TE events detected by MRI in this low thromboembolic risk population. Women were underrepresented. Calculation of the sample size was mainly based on events from cardiac interventional procedures, as no other data were available when the study protocol was written. This calculation may have overestimated the risk of silent TE events. Moreover, initiation of OAC after CV in 18.6% of the population may be a confounding factor. The observed changes in inflammatory and coagulation biomarkers, although significant, were very small, underlining that the analysis of circulating biomarker should be interpreted with caution and used as hypothesis generating.

In **Study III**, the number of baseline echocardiographic assessments and ECG recordings during follow-up were underrepresented in the CV-cohort. This underrepresentation may have underestimated the predictive value of LAVI in the CV-cohort and effected the reverse atrial electrical remodeling analysis. Differences in AF recurrence monitoring between the two groups might also have underestimated the detection rate in the CV-cohort, affecting predictor analyses. Treatment of AF for rhythm control, was included as a factor in all predictive models and may potentially have a confounding effect, elevating performance.

In **Study IV**, detailed past history such as diabetes mellitus or previous stroke was not collected, thus the CHA_2DS_2-VASc score[56] or HATCH score[302] could not be assessed comparatively with other predictive models. Cardiovascular medication at admission or during hospitalization, were not documented and the possible effects on ECG measurements could not be evaluated. Systemic condition at the time of incident new-onset AF was not recorded; consequently, the timely relation between new-onset AF and MACE was unclear. Since telemetry was unavailable for all participants, silent AF may have been undetected, which may have affected the results.

7. Conclusion

The following conclusions can be deduced based on the results of this thesis:

Studies I and II

The absence of new acute silent lesion on the sequential brain MRI may suggest that patients with very low thromboembolic risk (according to CHA_2DS_2-VASc score) could be cardioverted without prior anticoagulation at a short time interval after arrhythmia onset. We observed a transient increase in the biomarker of cerebral damage. Additionally, a high incidence of chronic WMH lesions was observed and a significant association of CHA_2DS_2-VASc score and presence of WMH was found. After CV, LA mechanical stunning, followed by reverse functional remodeling in conjunction with the transiently higher level of inflammatory and coagulative biomarkers during AF might support the presence of an enhanced thrombogenicity even in patients with an inherent low risk of stroke. Moreover, the finding of a more pronounced mechanical stunning in patients with a history of AF further supports the concept of adequate anticoagulation pericardioversion even in patients with low CHA_2DS_2-VASc score.

Paper III

The novel Peq-time, automatically measured time from P-wave onset to the peak positive deflection in V1, independently predicted AF recurrence at 12-months, as compared to P-wave duration or PwTfV1. Machine learning models, combining basic characteristics, atrial specific echocardiographic and ECG parameters from the novel P-wave partitioning, had the highest predictive performance. These findings may have future important implications in predicting AF recurrences assisting physicians in individually-tailored AF rhythm control.

Paper IV

The novel Peq-time>33ms, PR-interval>190ms and PWD>115ms were comparable independent electrocardiographic predictors of AF in hospitalized Covid-19 patients. Advanced age, male sex, increasing body mass index as well as disease severity also independently predicted new-onset AF. Predictive models that included clinical variables and the ECG variables Peq-time or the PR-interval yielded the best balanced accuracy predicting new-onset AF. Identification of patients with higher risk of new-onset AF could potentially reduce the poor outcomes by enabling early surveillance and treatment.

8. Clinical implications

AF is the most common sustained arrhythmia in adults, with increasing prevalence and significant burden on healthcare systems.[20-22, 303] Considering the progressive nature of AF, a structured characterization of AF and integrated clinical management are recommended, as highlighted in the latest ESC Guidelines.[19]

Currently, oral anticoagulation should be initiated as soon as possible before cardioversion and should be continued for at least four weeks in patients with AF duration > 24 hours.[19] However, oral anticoagulation may be omitted in patients with very low stroke risk, if the duration of AF is under 24h.[19] In our studies (I and II), valuable information was presented; a slower or incomplete LA functional recovery, at 7-10 days after CV, in patients with prior history of AF, and a transient enhanced trombogenicity was observed. As the majority of thromboembolic events occur within ten days after cardioversion,[62] the temporal pattern of AF and the substrate severity[19] (biomarker assessment) could be implicated, in stroke risk assessment.

In the current thesis, atrial electrical remodeling was analyzed through the detailed study of the electrocardiographic P-wave and its components. We introduced a novel partitioning of the P-wave by the peak of the positive deflection and, through repeated ECG measures, could identify the P-wave static and the dynamic parts. The novel Peq-time independently predicted not only AF recurrence after rhythm control intervention but also new-onset AF in Covid-19 hospitalized patients; the cut-off value for Peq-time, over 33ms, was proved to be the same in both Study III and IV. It is unclear if this P-wave index represents or associates with the permanent and irreversible structural changes in the atria; this novel finding could be implicated in future research to identify possible associations with substrate severity[19] assessed by the presence and extent of left atrial fibrosis in cardiac MRI. Predictive models AF recurrence built on patient characteristics, echocardiographic and atrial specific ECG variables could be clinically implemented in individually-tailored AF management.

New-onset AF in hospitalized Covid-19 patients, is associated with poor in-hospital outcomes.[171-175] Study IV was the first study to identify independent ECG predictors of new-onset AF in Covid-19 patients. Our findings can be clinically implemented to identify Covid-19 patients with higher risk of

new-onset AF, potentially reducing the poor outcomes by enabling early surveillance and treatment.

Inflammation and its associated immune response are involved in the initiation and maintenance of AF, not only in Covid-19 but also in other viral pneumonias and sepsis,[158, 159, 170, 296-299, 300] Our findings may be generalized and implemented to predictive models for new-onset AF in severe infections, models that include besides patient characteristics, atrial specific ECG measures and measures of disease severity i.e admission to intensive care or respiratory / circulatory support.

9. Summary in Swedish

Förmaksflimmer är den vanligaste ihållande arytmin hos vuxna och är förknippad med risk för stroke, kognitiv försämring, tysta cerebrala lesioner, hjärtsvikt, frekventa och långvariga sjukhusvistelser samt ökad mortalitet. Förmaksflimmer kännetecknas av snabb och okoordinerad elektrisk aktivitet i förmaken, vilket leder till förmaksremodellering. Den initiala elektriska remodelleringen på cellulär nivå och påverkan av extracellulärt matrix resulterar i försämrad förmaksfunktion, funktionell remodellering, förmaksstunning och slutligen strukturell remodellering, vilket leder till gradvis förmaksdilatation och dysfunktion, vilket främjar trombogenicitet.

Peroral antikoagulantiabehandling rekommenderas för primärprevention av tromboemboliska händelser vid förmaksflimmer, efter stratifiering av strokerisken med hjälp av CHA_2DS_2-VASc-score. Förbehandling med antikoagulantia används för närvarande före elektiv kardioversion av patienter med ihållande förmaksflimmer, men vid förmaksflimmer av kort duration (<48 timmar) hos patienter med låg strokerisk kan kardioversion utföras utan förbehandling med antikoagulantia.

Behandling av förmaksflimmer genom att återställa normal sinusrytm är mycket effektivt för symptomlindring. För närvarande rekommenderas farmakologisk eller elektrisk kardioversion av flimmer i akutskedet och antiarytmisk läkemedelsbehandling och- / eller kateterablation (isolering av lungvenerna, PVI) för att upprätthålla sinusrytmen över tid. Återställande av sinusrytmen resulterar i gradvis reversering av den elektriska och funktionella förmaksremodelleringen. Graden av omvänd remodellering är dock beroende av flimmerepisodens duration och förekomsten av irreversibla strukturella förändringar. Förmaks-stunningen och återhämtning av förmaksfunktionen anses bidra till utvecklingen av tysta eller kliniska cerebrovaskulära händelser, eftersom majoriteten av dessa inträffar inom tio dagar efter återställande av sinusrytmen. Effekten på den trombogena miljön, kognitiv funktion eller på förekomst och timing av nya tysta tromboemboliska händelser vid förmaksflimmer som konverteras inom 48 h, hos antikoagulantia-naiva patienter, är dock ännu outforskad.

Trots att effektiviteten av rytmkontrollerande strategier som kardioversion och PVI med eller utan antiarytmisk läkemedelsbehandling för förmaksflimmer är hög, är risken för återfall fortfarande inte försumbar. Flera kliniska variabler, inklusive typ av förmaksflimmer, hypertoni, hjärtsvikt, ålder och

vänster förmaksvolym, har identifierats som prediktorer för återfall. Dessutom har elektriskt remodellering av förmaken, mätt som förlängd P-vågduration, ökad P-vågs dispersion, minskade s.k."terminal forces" av P-vågen i avledning V1 samt vänsterförskjutning av P-vågens frontalaxel på elektrokardiogram (EKG), använts som prediktorer för förmaksflimmeråterfall. Den prediktiva kapaciteten hos EKG-prediktorer är dock svag. Ekokardiografiska prediktorer som speglar förmaksremodellering kan vara tidskrävande och mödosamma att bedöma, vilket begränsar rutinmässig användning vid hantering av patienter med förmaksflimmer.

Det allvarliga akuta respiratoriska syndromet coronavirus 2 som orsakar coronavirus sjukdom 2019 (Covid-19) har resulterat i miljontals dödsfall, världen över. Även om Covid-19 främst påverkar luftvägarna, är det också associerat med kardiovaskulära komplikationer. Nydebuterat förmaksflimmer har rapporterats som den vanligaste rytmrubbningen hos sjukhusvårdade Covid-19-patienter och är associerad med sämre kliniskt utfall under sjukhusvistelsen. Identifiering av patienter med högre risk för debut av förmaksflimmer kan potentiellt bidra till att påverka den försämrade prognosen genom att möjliggöra tidig upptäckt och behandling.

Syftet med denna avhandling var (i) att undersöka förekomsten och timingen av nya tysta tromboemboliska händelser efter kardioversion av förmaksflimmerepisoder av kort duration och studera flimmers och kardioversionens effekt på kognitiv funktion och biomarkörer för cerebral skada, (ii) att bedöma effekterna av ett kortvarigt förmaksflimmer och kardioversion på trombogenicitet genom att analysera förmakens hemodynamik med ekokardiografi och biomarkörer relaterade till hyperkoagulabilitet, samt att utforska om tidigare förmaksflimmer i anamnesen påverkar graden av återhämtning av förmaksfunktion, (iii) att identifiera nya EKG-prediktorer för förmaksflimmeråterfall, lämpliga för automatiska mätningar, att utvärdera dessa i prediktiva modeller och att studera omvänd/reverserad elektrisk förmaksremodellering genom seriella EKG-mätningar, (iv) att utvärdera traditionella och nya EKG- och kliniska prediktorer för nydebuterat förmaksflimmer hos sjukhusvårdade Covid-19-patienter, att utvärdera prediktiva modeller för nydebuterat förmaksflimmer vid Covid-19 och att utforska inverkan av nydebuterat förmaksflimmer på kliniska utfall under sjukhusvistelsen.

Artikel I och II baserades på en prospektiv kohort av antikoagulant-naiva patienter med förmaksflimmer som genomgick elektrisk kardioversion inom 48 timmar från debut. Inga akuta tysta cerebrala lesioner kunde identifieras på sekventiella magnetresonanstomografier av hjärnan. En högre förekomst av hyperintensiteter i vit substans observerades, och dessa var associerade med CHA_2DS_2-VASc-score. Vi observerade en mindre, tillfällig ökning av biomarkör för cerebral skada (S-100). Patienter med sedan tidigare konstaterat persisterande förmaksflimmer uppvisade sämre kognitiva funktionstestresultat. Vänster förmaksstunning observerades efter kardioversion och omvänd funktionell remodellering var långsammare eller ofullständig hos patienter

med tidigare förmaksflimmeranamnes. Tillfälligt högre nivåer av inflammatoriska och koagulationsrelaterade biomarkörer observerades innan kardioversion.

Studie III baserades på patienter med icke-permanent symptomatisk förmaksflimmer som hade genomgått rytmkontrollintervention, antingen elektrisk kardioversion eller ablationsbehandling med lungvensisolering, och följts upp i tolv månader. Den nya EKG variabeln *Peq-time*, tid från P-vågsstart till den maximala positiva deflektionen (>33 ms), var en oberoende prediktor av förmaksflimmeråterfall vid 12 månader efter rytminterventionen. Dessutom visade *P-leftward-area*, området från den maximala positiva deflektionen till slutet av P-vågen, störst förändring under uppföljningen och beskrev omvänd/reverserad elektrisk förmaksremodellering. Maskininlärnings prediktiva modeller som förutom kliniska variabler inkluderade förmaksspecifika ekokardiografiska och EKG- variabler gav hög prediktiv kapacitet.
Studie IV var en fördefinierad substudie i en internationell kohortstudie med vuxna patienter som var inlagda på sjukhus pga Covid-19 och som hade digitalt sparade EKG tillgängligt vid inläggningen. Patienter med tidigare anamnes på förmaksflimmer uteslöts från denna delstudie. Uppföljningsperioden för studien definierades som den tid patienterna var inlagda på en Covid-19-vårdenhet. Studie IV identifierade flera oberoende prediktorer för nytillkommet förmaksflimmerhos inlagda Covid-19-patienter, inklusive den nya parametern Peq-tid >33 ms, PR-intervall >190 ms och P-vågs duration (PWD) >115 ms. Andra faktorer som inläggning på intensivvårdsavdelning (IVA), behov av respiratoriskt stöd, hög ålder, manligt kön och förhöjt BMI predikterade också oberoende nytillkommet förmaksflimmer. Logistiska regressionsmodeller som inkluderade ålder, kön, BMI, inläggning på IVA och ovannämnda EKG-prediktorer visade mycket god prediktiv prestanda, och modellerna som inkluderade Peq-tid eller PR-intervall hade bäst balanserad noggrannhet.

Sammanfattningsvis kunde inga nya tysta hjärnlesioner detekteras efter kardioversion av flimmer med kort duration, men en hög förekomst av hyperintensiteter i vit substans observerades. Även om vänster förmak återhämtat sig inom tio dagar efter kardioversionen, förblev tömningsfraktionen av vänster förmak signifikant lägre hos patienter med tidigare historik av förmaksflimmer. Inflammatoriska och koagulativa biomarkörer var förhöjda under flimmer, innan kardioversionen, vilket tillsammans kan tyda på en ökad trombogenicitet, även hos dessa lågriskpatienter, vilket ytterligare stöder konceptet med adekvat antikoagulation i samband och efter kardioversion.

Den automatiskt mätta tiden från P-vågens början till den maximala positiva deflektionen i V1 predikterade återfall av förmaksflimmer bättre än P-vågens duration eller PwTfV1. Maskininlärningsmodeller som kombinerade kliniska variabler, förmaksrelaterade ekokardiografiska och EKG- parametrar hade bäst prediktiv prestanda. Dessa resultat kan ha viktiga implikationer för

att förutsäga återfall av förmaksflimmer och hjälpa läkare att anpassa behandlingen för varje individ.

De nya EKG-prediktorerna Peq-time>33ms, PR-interval>190ms och PWD>115ms var jämförbara oberoende prediktorer för nydebuterat förmaksflimmer hos inlagda Covid-19-patienter. Hög ålder, manligt kön, högt BMI samt sjukdomens svårighetsgrad predicerade också oberoende debut av förmaksflimmer under vårdtiden. Prediktionsmodeller som inkluderade kliniska variabler och EKG-variablerna Peq-time eller PR-interval hade bäst balanserad noggrannhet för att förutsäga ny debut av förmaksflimmer. Identifiering av patienter med högre risk för förmaksflimmer kan potentiellt förbättra prognosen genom att möjliggöra tidig övervakning och behandling.

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