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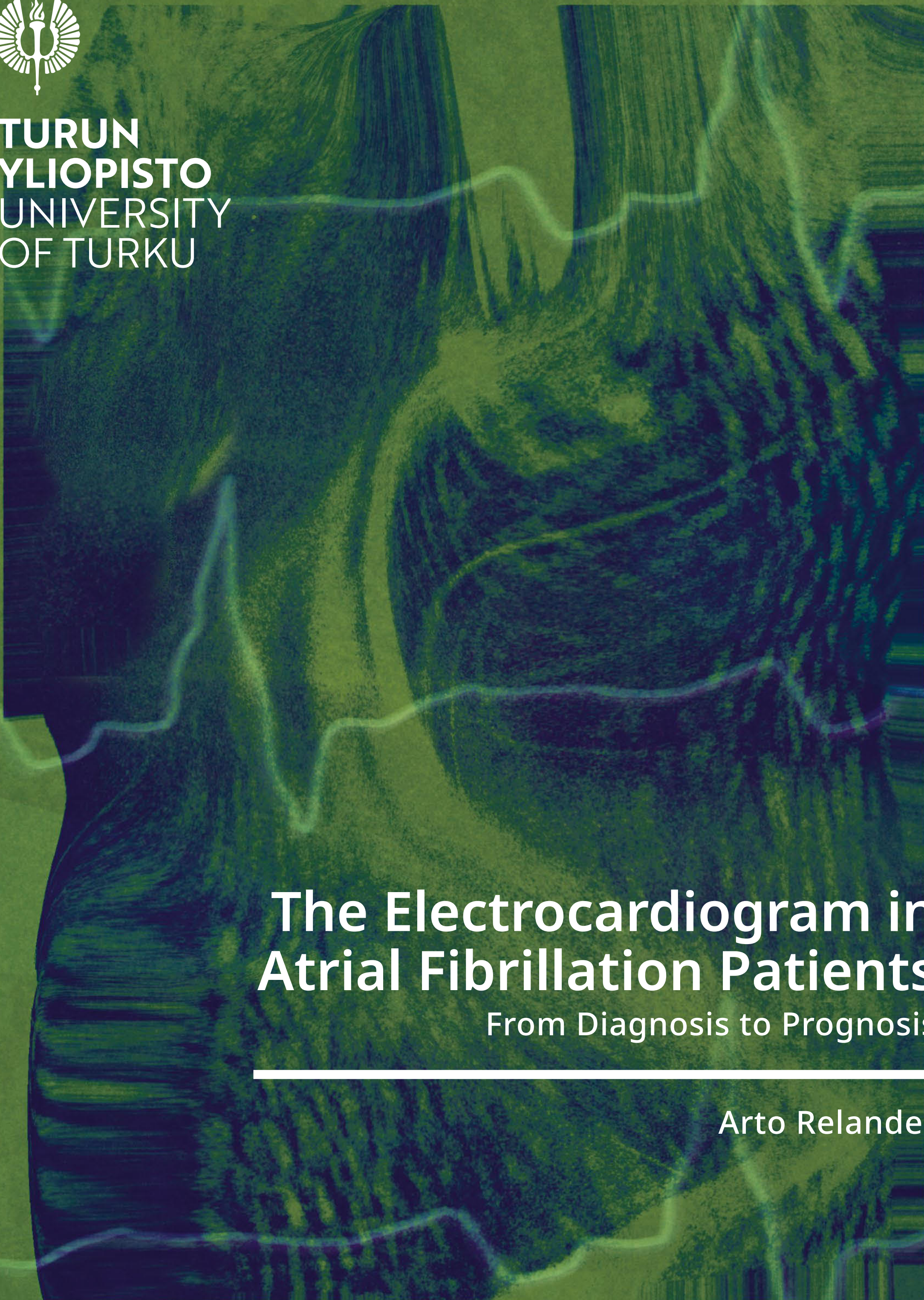

The Electrocardiogram in Atrial Fibrillation Patients

From Diagnosis to Prognosis

Arto Relander

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To my father

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ABSTRACT

Abnormal structural, functional, and electrophysiological properties in the atrial myocardium contribute to the development of atrial fibrillation (AF) and its complications. Several risk factors—such as older age and chronic cardiovascular diseases—have been identified for this pathological progression, yet limited methods exist to monitor the manifestation and evolution of the underlying atrial cardiomyopathy in clinical practice. The electrocardiogram (ECG) offers a non-invasive tool that may reflect these atrial properties through changes in the P-wave, which have been associated with AF incidence, rhythm control failure, and adverse cardiovascular outcomes.

This thesis aimed to identify P-wave parameters that predict ineffective cardioversion (CV) of AF, to improve patient selection thus minimizing procedural risks (I). It further evaluated whether P-wave features are associated with the risk of short- and long-term stroke or systemic embolism (SSE), particularly among patients classified as low risk by conventional methods (II). Finally, it assessed the temporal stability and progression of P-wave parameters to determine their reliability for risk stratification (III).

Patients with prolonged P-wave and a biphasic waveform had over fourfold higher odds of CV failure and threefold higher odds of early AF recurrence compared to those with normal P-waves (I). Similarly, the combination of various extensive abnormalities was associated with over a fivefold increase in odds for SSE within 30 days after CV and a fourfold increase in long-term SSE risk. Moreover, the presence of this composite variable doubled the risk of mortality and tripled the odds of heart failure during follow-up (II). Over a series of ECGs, nearly 75% of all P-wave abnormalities remained stable or progressed to a more severe form, with progression most evident among patients with the longest follow-up.

In conclusion, assessing the ECG of AF patients may aid in clinical decision-making by identifying those unlikely to benefit from CV and those at increased risk for AF-related complications. P-wave parameters appear stable or progressive over time, suggesting that even ECGs recorded prior to the onset of AF may be valuable in patient management.

KEYWORDS: atrial cardiomyopathy, atrial fibrillation, cardioversion, electrocardiogram, P-wave

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TIIVISTELMÄ

Poikkeavat rakenteelliset, toiminnalliset ja sähköiset ominaisuudet sydänlihaksessa altistavat eteisvärinän kehittymiselle ja lisäävät eteisvärinän komplikaatioiden mahdollisuutta. Korkea ikä sekä krooniset sydän- ja verisuonisairaudet myötävaikuttavat näihin patologisiin piirteisiin, joita on kuvattu käsitteellä eteiskardiomyopatia. Kliinisessä käytössä eteiskardiomyopatian ilmenemisen ja etenemisen arviointiin on rajallisesti keinoja, joista sydänfilmi (12-kytkentäinen EKG) on potentiaalinen vaihtoehto näiden sydänlihaksen poikkeavuuksien tutkimiseksi. EKG:n P-aalto kuvastaa sydämen eteisiä ja useita P-aallon piirteitä onkin yhdistetty eteisvärinän ilmaantumiseen, rytminhallinnan epäonnistumiseen ja rytmihäiriön komplikaatioihin.

Tämän väitöskirjan tavoitteena oli etsiä P-aaltomuutoksia, joiden avulla voitaisiin tunnistaa potilaat, jotka eivät hyödy eteisvärinän sähköisestä rytminsiirrosta (I). Lisäksi arvioitiin, liittyvätkö P-aaltomuutokset eteisvärinän tromboembolisiin komplikaatioihin lyhyellä- tai pitkällä aikavälillä rytminsiirron jälkeen erityisesti potilailla, jotka perinteisesti luokiteltaisiin matalan riskin ryhmään (II). Lopuksi tutkittiin P-aaltomuutosten pysyvyyttä ja kehittymistä pitkäaikaisseurannassa toistuvien EKG-mittausten avulla (III).

Potilailla, joiden P-aalto oli pidentynyt ja poikkevan muotoinen havaittiin yli nelinkertainen todennäköisyys rytminsiirron epäonnistumiseen ja kolminkertainen todennäköisyys eteisvärinän varhaiseen uusiutumiseen (I). Vastaavasti vahvoihin P-aallon pituuden ja muodon muutoksiin liittyi yli viisinkertainen tromboembolian vaara kuukauden kuluessa rytminsiirrosta, riskin ollessa nelinkertainen pitkän aikavälin seurannassa. Lisäksi muutokset kaksinkertaistivat riskin kuolla ja kolminkertaistivat sydämen vajaatoiminnan kehittymisen todennäköisyyden seuranta-aikana (II). Noin 75 % P-aaltomuutoksista säilyi joko ennallaan tai vaikeutui useiden peräkkäisten EKG-tutkimusten sarjassa. P-aaltomuutokset lisääntyivät useammin seuranta-ajan pitkittyessä (III).

P-aaltomuutosten tunnistaminen ja arviointi eteisvärinäpotilaan EKG:sta voi tukea kliinistä päätöksentekoa auttamalla tunnistamaan potilaat, joille rytminsiirto on todennäköisesti hyödytön tai joilla on kohonnut riski eteisvärinän komplikaatioihin. P-aaltomuutosten pysyvyys voi mahdollistaa aiemmin kertyneiden EKG-rekisteröintien käytön eteisvärinän riskiarviossa.

AVAINSANAT: eteiskardiomyopatia, eteisvärinä, rytminsiirto, sydänfilmi, P-aalto

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Abbreviations

AAD	antiarrhythmic drug
ABC	atrial fibrillation better care
aCM	atrial cardiomyopathy
AF	atrial fibrillation
AF-CARE	atrial fibrillation—comorbidity and risk factor management, avoid stroke and thromboembolism, reduce symptoms by rate and rhythm control, evaluation and dynamic reassessment
AIAB	advanced interatrial block
ANP	atrial natriuretic peptide
ATRIA	Anticoagulation and Risk Factors in Atrial Fibrillation
AUC	area under the curve
BNP	brain natriuretic peptide
CHA_2DS_2-VA	congestive heart failure, hypertension, age $\geq$ 75 years (doubled), diabetes, and prior stroke, transient ischemic attack or thromboembolism (doubled), vascular disease, age 65–74 years
CHA_2DS_2-VASc	congestive heart failure, hypertension, age $\geq$ 75 years (doubled), diabetes, and prior stroke, transient ischemic attack or thromboembolism (doubled), vascular disease, age 65–74 years, sex category (female)
CI	confidence interval
CT	computed tomography
CV	cardioversion
GARFIELD-AF	global anticoagulant registry in the field–atrial fibrillation
DOAC	direct oral anticoagulant
ECG	electrocardiogram
ECM	extracellular matrix
EAM	electroanatomic mapping
F-wave	fibrillatory wave
FinCV	Finnish cardioversion

HAS-BLED	hypertension, abnormal renal or liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (age ≥ 65 years), drugs/alcohol concomitantly
HR	hazard ratio
LA	left atrium
LAA	left atrial appendage
MRI	magnetic resonance imaging
MVP	morphology–voltage–P-wave duration
OAC	oral anticoagulant
OR	odds ratio
PET-CT	positron emission tomography–computed tomography
PTF	P-terminal force
PWA	P-wave abnormality
ROC	receiver operating characteristic
SD	standard deviation
SR	sinus rhythm
SSE	stroke or systemic embolism
QoL	quality of life

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Relander A., Hellman T., Vasankari T., Nuotio I., Airaksinen K. E. J., Kiviniemi T. (2021). Advanced interatrial block predicts ineffective cardioversion of atrial fibrillation: a FinCV2 cohort study. *Annals of Medicine*, 53(1), 722–729. https://doi.org/10.1080/07853890.2021.1930139

II Relander A., Ruohonen I., Jaakkola S., Vasankari T., Nuotio I., Airaksinen K. E. J., Kiviniemi T. (2024). Novel electrocardiographic classification for stroke prediction in atrial fibrillation patients undergoing cardioversion. *Heart Rhythm*, 21(12), 2407–2418. https://doi.org/10.1016/j.hrthm.2024.04.083

III Relander A., Kääriä J., Jaakkola S., Vasankari T., Nuotio I., Airaksinen K. E. J., Kiviniemi T. (2025). Prevalence and progression of P-wave abnormalities in patients with atrial fibrillation. *Heart Rhythm*. Advance online publication. https://doi.org/10.1016/j.hrthm.2025.03.1981

1 Introduction

Palpitations, sudden onset of dyspnea, and fatigue are common initial presentations of atrial fibrillation (AF), resulting from the characteristic rapid, irregular rhythm. While the symptoms are often perceived as alarming, an AF episode usually poses no immediate threat. However, in the long-term, a history of AF is associated with a significant risk of mortality and morbidity, particularly due to thromboembolic complications. With its increasing prevalence in the aging population, AF represents a global health challenge, highlighting the need for a deeper understanding of the underlying mechanisms to further improve management.

The risk of stroke or systemic embolism (SSE) is increased fivefold by AF, with an annual complication rate ranging between 0.2% and 20% without treatment. Fortunately, oral anticoagulant (OAC) drugs reduce SSE risk by two-thirds, making them the standard preventive therapy. However, effective implementation of OAC therapy relies on timely diagnosis of AF. Early detection of AF is often challenging, as at first, AF typically presents as short and random paroxysms and remains asymptomatic in many patients. Moreover, OAC therapy is reserved for patients with a moderate to high SSE risk to balance the benefits of stroke prevention against the inherent risk of bleeding. While risk stratification is recommended by guidelines internationally, existing tools have limitations, and some low-risk patients still suffer from SSE, underscoring the need for more precise predictive approaches.

Atrial cardiomyopathy (aCM) is a syndrome of electromechanical changes in the atrial myocardium that may contribute to the development of AF, and in turn, AF can exacerbate aCM by creating a cycle of electrical, structural, and functional remodeling. These alterations may clinically present as the progression of AF, typically from short episodes to a persisting and eventually permanent arrhythmia that resists attempts to restore normal sinus rhythm (SR). According to current consensus, aCM diagnosis is limited to histopathological findings, thereby limiting its applicability in clinical practice. Electrocardiographic (ECG) markers of abnormal atrial conduction have been associated with features of aCM and have thus been proposed as potential markers for its detection. Notably, some of these P-wave indices have also been linked to an increased risk of SSE, suggesting that aCM itself may play a role in cardiac thrombosis.

This thesis investigates the standard ECG as a tool to enhance risk stratification and guide treatment decisions in patients with AF. First, the ECGs of AF patients undergoing elective electrical cardioversion (CV) were assessed to explore the initial outcome of the rhythm control procedure as well as the later recurrence of AF. The supplementary role of ECG in SSE risk analysis was then explored by identifying potential P-wave parameters in patients with a post-CV SSE and then validating the results with long-term outcomes. Finally, a longitudinal analysis utilizing three successive ECGs from known AF patients examined P-wave evolution over time.

2 Review of the Literature

2.1 Atrial fibrillation

2.1.1 Epidemiology and clinical significance

AF is the most common chronic arrhythmia, with a lifetime risk of up to 30% after age 55 (Vinter et al., 2024). The condition is highly age-dependent, affecting 0.1% of individuals under 55 and over 10% of those above 75 (Go et al., 2001; Heeringa et al., 2006). Global prevalence has nearly doubled in less than a decade, rising from 33.5 million (0.5%) in 2010 to 59.7 million (0.8%) in 2019, with aging believed to be the primary driver (Chugh et al., 2014; H. Li et al., 2022). Similarly in the United States, the number of cases tripled in the last five decades preceding the 21st century and are projected to double again between 2010 and 2030 (Colilla et al., 2013; Schnabel et al., 2015). Additionally, more than 10–20% of all AF patients remain undiagnosed, owing to the paroxysmal nature of the arrhythmia and the absence of symptoms in some individuals (Turakhia et al., 2023). Nevertheless, recent studies utilizing multiple comprehensive registries estimated a national prevalence of 4.5% in the United States and 5.2% in Finland among adults aged 20 years and older, significantly exceeding previous estimates (Lehto et al., 2022; Noubiap et al., 2024).

Similar to prevalence, incidence rate increases with age, from 0.1–0.4 per 1,000 person-years in individuals under 55 years up to 17.3-31.9 per 1000 person-years in those over 75 (Heeringa et al., 2006; Lane et al., 2017; Lehto et al., 2022). Globally, the number of new AF cases has risen markedly from 2.7 million in 2010 to 4.7 million in 2019. However, despite this increase in absolute cases, the incidence rate remained relatively stable, at 69 and 74 per 100,000 person-years, respectively (Chugh et al., 2014; H. Li et al., 2022). The rise in both incidence and prevalence has been attributed to increased life expectancy, the accumulation of other risk factors, and improved methods of detection (E. Y. Ding et al., 2020; Kornej et al., 2020; Linz et al., 2024).

The risk of AF varies according to sex, race, lifestyle and comorbidities (Kornej et al., 2020; Staerk et al., 2017). Men have a 50% higher risk for developing AF and the prevalence is approximately twofold higher compared to women (Schnabel et al., 2015). Although men tend to develop AF earlier in life, the lifetime risk for AF is similar across sexes (Magnussen et al., 2017) The effect of black, Hispanic or Asian ethnic background lowers the risk of AF compared to whites, especially in the absence of other risk factors, though the underlying mechanism remains unclear (Dewland et al., 2013; Rodriguez et al., 2015). The association between physical activity and AF is complex. On one hand, a sedentary lifestyle and obesity increase the likelihood for AF incidence, and they also promote other AF-related risk factors and comorbidities (Huxley et al., 2011; Thorp et al., 2011). On the other hand, lifelong activity in high-intensity endurance sports is associated with a nearly fourfold increase in the odds of AF compared to inactive individuals, whereas life with moderate activity appears to reduce the odds by two-thirds (Calvo et al., 2015). Smoking is another important modifiable lifestyle risk factor, demonstrating a dose-dependent relationship with AF incidence (Chamberlain et al., 2011). Overall, active smoking increases the risk by 1.4–2 times compared to non-smokers (Alonso et al., 2013; Chamberlain et al., 2011). Importantly, second-hand exposure to smoking in childhood or gestational development is associated with nearly 40% increased AF risk later in life (Dixit et al., 2016).

Hypertension, heart failure, coronary artery disease, and diabetes are among the most significant comorbidities contributing to AF development (Alonso et al., 2013; Schnabel et al., 2015). Although the relative increase in AF risk associated with each condition individually is modest, varying between 1.2 and 2 times higher, their high prevalence in the general population means they account for a considerable proportion of cases of AF (Allan et al., 2017; Alonso et al., 2013; Schnabel et al., 2015). In a prospective study with 17 years of follow-up on average, 57% of incident AF could be attributed to hypertension, coronary artery disease, diabetes, smoking, and obesity (Huxley et al., 2011). Increasing evidence suggests that effective treatment of the risk factors could work in both primary and secondary prevention of AF (Elliott et al., 2023; Van Gelder et al., 2024). For instance, intensive blood pressure treatment to a systolic blood pressure target of < 120 mmHg instead of < 140 mmHg resulted in 26% lower risk of new-onset AF (Soliman et al., 2020). Furthermore, many of the risk factors also predispose to AF-related complications, particularly SSE, highlighting the importance of managing these comorbidities (Van Gelder et al., 2024).

The clinical significance of AF lies primarily in its association with increased morbidity, disability, and mortality. AF introduces a fivefold risk for SSE, and conversely, one in five strokes is associated with AF (Lamassa et al., 2001; Wolf et al., 1991). Moreover, AF-related strokes are often more severe, predisposing to long-term disability and mortality, compared to strokes from other aetiologies (Jørgensen et al., 1996; Lamassa et al., 2001). Additionally, nearly half of AF patients develop heart failure over time (T. J. Wang et al., 2003), with meta-analyses reporting nearly fivefold increase in risk (Odutayo et al., 2016; Ruddox et al., 2017). The impact of heart failure is reflected in the increased rate of hospitalizations in AF patients, as one in three AF patients require inpatient care each year (Christiansen et al., 2013; Steinberg et al., 2014). Over two-thirds of emergency department visits related to AF turn into hospital admissions (Rozen et al., 2018), and overall, 6.8% of all hospital admissions are associated with AF (Christiansen et al., 2013). Furthermore, AF is associated with a twofold risk for all-cause death (Ruddox et al., 2017), and the risk is most pronounced in the elderly: among Medicare beneficiaries, 80 years old on average, one in five died within a year of AF diagnosis and nearly half during the first five years (Piccini et al., 2014).

The economic impact of AF is, in large part, driven by hospitalizations, accounting for more than 40% of the total AF-related healthcare costs, on average (Jönsson et al., 2010; Ringborg et al., 2008). In a multi-national European study, the average annual total cost of an AF patient ranged from €1,010 to €3,225 depending on the country, while the mean expenses of an inpatient admission were estimated between €1,363 and €6,320 (Ringborg et al., 2008). In Sweden, hospitalizations due to AF related strokes were found more expensive than those from other etiologies (€10,192 vs. €9,374), owing to longer stays and more complications (Ghatnekar & Glader, 2008). Overall, the additional healthcare costs associated with AF are substantial: working-age adults with AF incurred an average of $38,861 in medical expenses, compared to $28,506 for those without AF (Turakhia et al., 2015). Total annual healthcare costs attributable to AF in Denmark varied between €194 million and €263 million, accounting for 1.3–1.7% of all healthcare expenditure (Johnsen et al., 2017), while a similar estimate of 0.9–2.4% was calculated in the United Kingdom (Stewart et al., 2004).

The growing prevalence and significant clinical and economic impact of AF highlight the need for effective detection and management to address this global health challenge (Van Gelder et al., 2024).

2.1.2 Diagnosis and screening

The diagnosis of AF is based on detecting the characteristic disorganized atrial activation and the resulting irregular ventricular contractions which are discernible in the standard 12-lead ECG. In a typical recording (Figure 1), the atrial P-waves are replaced by continuous fibrillatory waves (F-waves), and the intervals between ventricular QRS complexes vary in duration (Van Gelder et al., 2024). Combined with a typical history of fatigue, dyspnea or palpitations, the diagnosis is usually straightforward (Abu et al., 2022). However, the complete absence of symptoms or sudden termination of an episode might delay the diagnosis.

Usually, AF presents at first in short, infrequent episodes that may become longer and more frequent over time (Joglar et al., 2024). Up to 90% of patients have recurrent AF episodes within two years of the initial onset (Israel et al., 2004). A meta-analysis estimated the annual rate of progression between 7.1% and 18.6%, depending on the type of AF (Blum et al., 2019). The clinical presentation often dictates its classification into paroxysmal, persistent, or permanent forms; however, individuals can alternate periodically between categories (Joglar et al., 2024; Van Gelder et al., 2024). While these definitions are descriptive of the disease pattern, they also determine AF treatment strategies. A paroxysmal AF terminates within 7 days with or without intervention, whereas in persistent AF, self-restoration of SR is not expected, but intervention may be attempted. AF is determined permanent if rhythm control strategies have proven ineffective, or restoring SR is not otherwise feasible (Van Gelder et al., 2024). The risk of SSE is evident regardless of the disease pattern (Banerjee et al., 2013).

Although ECG is a readily available test, it cannot detect AF if the episode has receded by the time of recording. This diagnostic challenge underscores the need for extended monitoring and active screening to prevent future complications, though no method has been proven superior to opportunistic pulse palpation during physical examination (Davidson et al., 2022). Various monitors enable continuous ECG tracing for longer periods, with novel approaches emerging. However, the benefits seem to largely depend on screening duration and patient selection (Mairesse et al., 2017). Applicability for screening could be assessed by using different prediction models that utilize previously discussed risk factors (Himmelreich et al., 2020). Currently, the American guidelines do not recommend AF screening—in the absence of supporting evidence—but support prolonged monitoring after a stroke of unknown source (Joglar et al., 2024). The European guidelines, however, recommend active screening in patients at elevated stroke risk, though recommended methods vary from pulse palpation to invasive monitoring (Van Gelder et al., 2024).

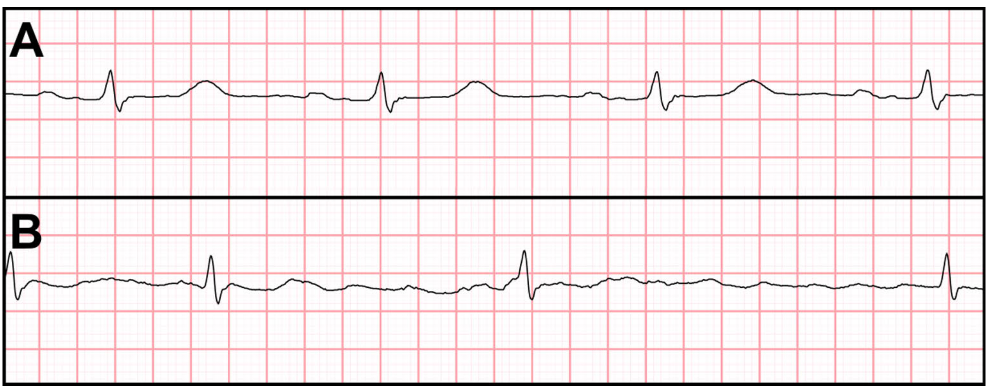

Figure 1. Sample electrocardiograms from a single patient. Panel A depicts normal sinus rhythm with regular QRS complexes preceded by P-waves. Panel B shows irregular QRS intervals and a coarse fibrillatory baseline, consistent with atrial fibrillation.

Trials have demonstrated higher rates of AF detection using either repeated ECGs or continuous monitoring with different devices, but the usability of these methods is reduced by false-positives and in patients with short, infrequent episodes of subclinical AF, who are at lower risk of SSE (Elbadawi et al., 2022; Svendsen et al., 2021). A systematic review concluded that single time-point screening with pulse palpation or ECG detects previously unknown AF in 1.0% of the general population and in 1.4% of patients older than 65 years (Lowres et al., 2013). With 72 hours of continuous ambulatory Holter ECG monitoring, new AF was detected in 4.3% of patients with a recent stroke or transient ischemic attack (Grond et al., 2013). Similarly, in the LOOP[a] trial, implantable recorders detected AF in 31.8% of cases, compared to 12.2% with standard care, over a 3-year period in subjects with at least one risk factor for AF (Svendsen et al., 2021). Newer technologies, including handheld and wearable devices, are less invasive and burdensome alternatives but mostly lack validation in a clinical setting (Lopez Perales et al., 2021). Repeated 30-second measurements with a handheld single-lead ECG revealed new AF in 3.0% of the elderly participants in the Swedish STROKESTOP study (Svennberg et al., 2021), while single 30-second measurements with a similar device identified new cases in 1.1% of the subjects in a Belgian population-wide screening programme (Proietti et al., 2016). Although STROKESTOP also demonstrated screening to be a cost-effective way of reducing AF-related complications (Lyth et al., 2023), the findings may not apply to younger, low-risk cohorts, owing to the additional tests and procedures they may require (Brandes et al., 2022). Despite early AF detection, no improvement in clinical outcomes was observed in the LOOP cohort (Svendsen et al., 2021).

Recent advances in consumer-based electronics have made rhythm monitoring accessible to nearly everyone in the form of smartphones and smartwatches, simultaneously increasing awareness of cardiac conditions (Perez et al., 2019; Vyas et al., 2024). Novel approaches usually utilize either single-lead ECG, photoplethysmography, or mechanocardiography for uninterrupted heart rate monitoring (Lopez Perales et al., 2021). With an increasing number of devices being cleared for AF detection by the The United States Food and Drug Administration (Hudock et al., 2024), current guidelines still suggest a 12-lead ECG or at least 30 seconds of continuous single-lead ECG recording for a definite AF diagnosis (Joglar et al., 2024; Van Gelder et al., 2024). In the Apple Heart study, a wrist-worn photoplethysmography device detected AF in 0.5% of over 400,000 adult participants during a median monitoring time of about 4 months, and the diagnosis

[a] LOOP: Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-risk Individuals

was subsequently confirmed in 34.0% of the reported cases (Perez et al., 2019). The Fitbit Heart study reported a 0.1% detection and 32.2% confirmation rates with a similar study setting and population (Lubitz et al., 2022). Importantly, only 23.9% and 17.3% of all device-detected AF in the respective studies led to the initiation of OAC, with both studies reporting an average participant age of under 50 years (Lubitz et al., 2022; Perez et al., 2019). While the accessibility and utility of these devices are promising, the findings suggest that screening efforts should target high-risk cohorts to help reduce overdetection and unnecessary testing or treatment (Lopez Perales et al., 2021).

2.1.3 Management

2.1.3.1 Overview

Management of AF involves reducing the risk of SSE, alleviating symptoms, and addressing comorbidities. Guidelines suggest frameworks, such as the AF-CARE that builds on the previously established ABC pathway, to systematically guide treatment and evaluation (Proietti et al., 2018; Van Gelder et al., 2024). Initial examination and further assessments can often be managed in an outpatient setting, although hospitalization may be required in cases of severe symptoms or hemodynamic instability.

It is vital to evaluate possible predisposing reversible factors upon AF diagnosis. Arrhythmia may be acutely triggered by precipitants such as severe infections, pulmonary embolism, or illicit drug use, and management of these conditions may reverse AF to SR and reduce the risk of long-term recurrence (Lin et al., 2022; Lubitz et al., 2015; Meierhenrich et al., 2010). Thyroid testing is warranted after incident AF even without suitable symptoms, as over 10% of hyperthyroid patients present with concurrent AF within a month of the diagnosis, and approximately two-thirds spontaneously revert to SR within months after reaching euthyroid state (Frost et al., 2004; Klein & Ojamaa, 2001). Similarly, as heavy alcohol consumption may induce AF, moderate consumption reduces the odds of recurrence (Marcus et al., 2021).

Identifying and addressing associated chronic conditions reduces overall disease burden, increases the efficacy of therapies, and improves long-term outcomes (Middeldorp et al., 2018; Pinho-Gomes et al., 2021). Considerable comorbidities are similar to AF risk factors discussed earlier, including cardiovascular conditions, diabetes, and obesity. For the most common diagnoses, medical history, physical examination, and blood tests are sufficient; however, transthoracic echocardiogram is recommended to detect any underlying structural or functional cardiac condition that could affect treatment or outcomes (Tops et al., 2010).

In addition to recommending medications, procedures, and lifestyle changes to effectively manage AF, guidelines also recommend patient education and shared decision making (Joglar et al., 2024; Van Gelder et al., 2024), as they have been proven to improve treatment adherence (P. J. Wang et al., 2023).

2.1.3.2 Stroke prevention

Thromboembolic complications are the leading cause of mortality and morbidity in patients with AF (Virani et al., 2020). On average, AF increases the risk of stroke fivefold (Wolf et al., 1991), with an annual average risk of 4.5%, and accounts for 20–30% of the nearly 8 million strokes occurring worldwide each year (Feigin et al., 2021; Marini et al., 2005; Virani et al., 2020). AF-related strokes are more severe leading to increase in-hospital and follow-up mortality compared to events from other sources (Vinding et al., 2022). Among AF patients, suffering a stroke triples mortality rate, and within one year up to 40% have deceased (Fang et al., 2014). Moreover, a prior stroke increases the risk for recurrent strokes 2.5-fold (Hart, Pearce, Albers, et al., 2007), but the risk appears to be lower if AF was diagnosed shortly after the first stroke (Romoli et al., 2025). While the correlation between AF and SSE has been established, the temporal relation and the exact pathophysiological mechanisms underlying thrombogenesis remain unclear (Brambatti et al., 2014; Choi et al., 2023).

Cardioembolism from the left atrial appendage (LAA) is the most prevalent cause of AF-related SSE (Katsi et al., 2019; Mahajan et al., 2012). Thrombus formation is a complex process occurring under the conditions best described by Virchow's triad: structural abnormalities, blood stasis, and hypercoagulability (W. Y. Ding et al., 2020). Under normal conditions, these criteria are not fulfilled, and physiological clotting regulation is maintained (Dahlbäck, 2000). However, the presence of these conditions in AF is well documented (W. Y. Ding et al., 2020). The basic principle and examples of underlying conditions are illustrated in Figure 2.

Dilation of the left atrium (LA) or LAA, endothelial damage, and fibrosis are examples of structural remodeling related to stroke, even in the absence of AF (Kamel & Healey, 2017). In many cases, these abnormalities precede AF emergence and are further exacerbated by the arrhythmia (M. Li et al., 2022). Chamber enlargement is accompanied by a reduction in muscle volume, with the muscle being replaced by fibrous and elastic tissue (Shirani & Alaeddini, 2000).

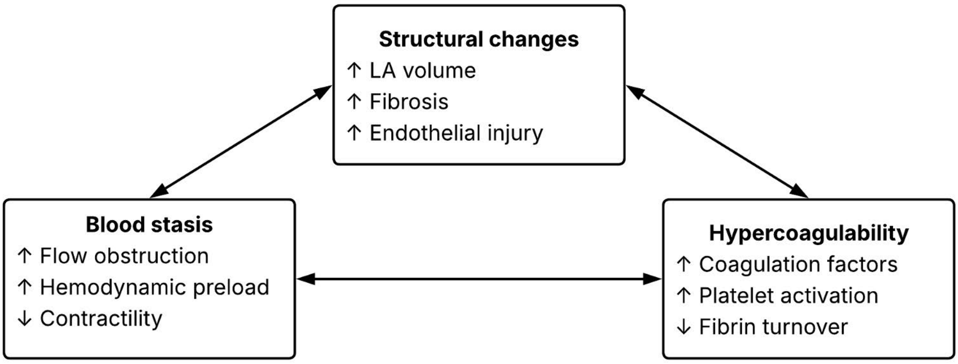

Figure 2. Mechanisms of thrombus formation in atrial fibrillation through Virchow's triad. Reference: (W. Y. Ding et al., 2020). Abbreviation: LA, left atrium.

Masawa et al. observed autopsy subjects and found a thickened, fibrous, and wrinkled endocardium exclusively in patients with AF, which strongly correlated with the presence of intramural thrombi (Masawa et al., 1993). Fibrotic changes, regulated in part by matrix metalloproteinase enzymes, seem to propagate as a reactive response to inflammation or pressure overload, or as a reparative reaction to the loss of cardiomyocytes (Kong et al., 2013). While atrial fibrosis was found an independent risk factor for thrombosis (Akoum et al., 2013), it may in fact be related to the dysregulation of matrix metalloproteinases affecting the coagulation cascade and platelet response (W. Y. Ding et al., 2020).

The inherent loss of contractility in AF combined with LA dilatation and fibrosis result in abnormal blood flow, promoting thrombogenesis (W. Y. Ding et al., 2020). Volume overload or mitral stenosis can further affect flow conditions (Watson et al., 2009). Blood stasis may be visualized in echocardiography by a smoke-like pattern—spontaneous echo contrast—especially in patients with abnormal atrial dimensions (Black et al., 1993). The phenomenon is significantly more common in AF patients and is associated with over twofold risk of stroke regardless of AF history (Kumagai et al., 2014; Vincelj et al., 2002). In vascular injury, impaired flow conditions may promote thrombosis by allowing other coagulation mechanisms to operate (W. Y. Ding et al., 2020).

The hypercoagulable state is driven by activation of the coagulation cascade, inappropriate platelet activation, and disturbed fibrinolysis, each of which is reflected by specific biomarkers (W. Y. Ding et al., 2020). Prothrombin fragment F1+2, fibrinogen, and von Willebrand factor are examples of overexpressed coagulation markers found at higher levels in AF patients compared to healthy controls (Mondillo et al., 2000; Turgut et al., 2006). Similarly, AF patients exhibit elevated β-thromboglobulin, P-selectin, and platelet factor 4, indicating increased platelet activity (Fu et al., 2011; Mondillo et al., 2000). Elevated D-dimer levels further suggest increased fibrin turnover, and plasminogen activator inhibitors mark impaired clot breakdown (Mondillo et al., 2000). Although some underlying mechanisms of hypercoagulability remain unclear, endothelial damage promotes the overexpression of von Willebrand factor and plasminogen activator inhibitors (Cai et al., 2002; Nakamura et al., 2003), while blood stasis further contributes by reducing von Willebrand factor degradation and increasing P-selectin levels (W. Y. Ding et al., 2020; Wysokinski et al., 2018), thus completing the self-propagating Virchow's triad.

Targeting the coagulation mechanism with OACs is the cornerstone of SSE prevention. Warfarin—in use since the 1950s—indirectly affects various coagulation factors and was found to normalize D-dimer levels but had no effect on fibrinogen or von Willebrand factor, suggesting it does not influence the underlying mechanisms (Hirsh et al., 2003; Lip et al., 1995). Nevertheless, warfarin therapy reduces stroke risk by two-thirds, while conversely increasing the bleeding risk by 1.5% per year (Hart, Pearce, & Aguilar, 2007; Lopes et al., 2013). In patients with moderate to high stroke risk, the benefits outweigh the risks; however, warfarin's usability is further limited by significant food and drug interactions as well as a narrow therapeutic range (Lopes et al., 2013; Van Gelder et al., 2024). Failures in dose adjustments can either reduce efficacy in SSE prevention, or further increase bleeding risk (Pandey et al., 2020). Unlike warfarin, newer direct OAC (DOAC) agents specifically inhibit either thrombin (dabigatran etexilate) or factor Xa (rivaroxaban, apixaban, edoxaban) to prevent thrombus formation (Connolly et al., 2009; Giugliano et al., 2013; Granger et al., 2011; Patel et al., 2011). They have demonstrated a further 19% reduction in SSE risk, with 52% fewer intracranial hemorrhages, and no significant difference in other major bleeding compared to warfarin (Carnicelli et al., 2022), making them a first-line option for SSE prevention (Joglar et al., 2024; Van Gelder et al., 2024). DOAC efficacy has been demonstrated in various subpopulations, including the elderly and those with heart failure or chronic kidney disease (Harrison et al., 2022; Malhotra et al., 2019; Savarese et al., 2016). Yet, patients with mechanical heart valves or moderate to severe mitral stenosis are still treated with warfarin, as DOAC patients suffered excess bleeding or SSE in randomized trials (Connolly et al., 2022; Eikelboom et al., 2013; T. Y. Wang et al., 2023).

By default, OAC therapy should be considered for all AF patients regardless of the arrhythmia presentation. However, the risk for thromboembolism is heterogeneous and depends on the accumulation of comorbidities and other factors. Given the increased chance of bleeding, OAC is only recommended to those at higher (approximately ≥ 2% annually) risk for thromboembolism, while individuals at intermediate risks (1–2% annually) require careful assessment to balance the outcomes (Joglar et al., 2024; Van Gelder et al., 2024). Generally, SSE risk is affected by the same factors that increase the likelihood of AF, increasing age being the most significant. Between the ages 65 and 74, the risk was 2.1 times higher than in younger patients, increasing to 2.8-fold in those over 75 and 6.9-fold in those over 85 (Noubiap et al., 2021). Similarly, in a recent meta-analysis, the annual SSE incidence rates were 1.2%, 1.5%, and 2.9% at ages 65, 75, and 85, respectively (Cheng et al., 2025). Previous strokes or transient ischemic attacks increase the risk 2.8 times, while hypertension, diabetes, heart failure, and vascular disease raise the risk between 1.2-fold and 1.6-fold (Noubiap et al., 2021). Simultaneously, the same factors contribute to the bleeding risk (Gorog et al., 2022).

Table 1. Validated models for evaluating stroke risk. Modified from: (Joglar et al. 2024).

	CHA_2DS_2-VA	ATRIA	GARFIELD-AF
Age 65–74 years	1	3	0.20
Age ≥75 years	2	5	0.59
Age ≥ 85 years		6	0.98
Female sex		1	
Hypertension	1	1	0.16
Renal disease		1	0.35
Diabetes	1	1	0.21
Current smoking			0.48
Congestive heart failure	1	1	0.23
Previous stroke or TIA	2	2–8*	0.80
Vascular disease	1		0.20
Dementia			0.51
Previous bleeding			0.30
Proteinuria		1	
Low risk score	0	≤ 5	≤ 0.89
Intermediate risk score	1	6	0.90–1.59
High risk score	≥ 2	≥ 7	≥ 1.60

* Age dependent points: 8 if < 65 years; 4 if 65-74 years; 2 if 75–84 years; 3 if ≥ 85 years.
Acronym CHA_2DS_2-VA indicates Congestive heart failure, Hypertension, Age ≥ 75 years (doubled), Diabetes, prior Stroke or TIA (doubled), Vascular disease, Age 65–74 years; ATRIA indicates Anticoagulation and Risk Factors in Atrial Fibrillation; GARFIELD-AF indicates Global Anticoagulant Registry in the Field-Atrial Fibrillation. Abbreviation: TIA, transient ischemic attack

Several tools (Table 1) have been developed to aid risk stratification in clinical practice, classifying patients into low, intermediate, or high SSE risk, based on common comorbidities and other known risk factors, facilitating a straightforward OAC initiation. The CHA_2DS_2-VASc is a widely used scoring system, which identifies low risk (0.2–0.4%/year) patients without the need for OAC at zero points (van Doorn et al., 2017; Van Gelder et al., 2024). The inclusion of a sex category has caused variation in the implementation of the system (Antonenko et al. 2017), as SSE risk was observed to be similar in males and females in the absence of other risk factors, yet more pronounced in women with older age or other risk factors (Mikkelsen et al., 2012; P. B. Nielsen et al., 2018). To address this disparity, guidelines recommended anticoagulation for males with two points and females with three (Joglar et al., 2024; Van Gelder et al., 2024), whereas the original system used two points for both (Lip et al., 2010). However, in a recent update, the European Society of Cardiology recommended a more streamlined version—the CHA_2DS_2-VA score—as the additional risk from female sex seems to have decreased over time (Van Gelder et al., 2024; Teppo et al., 2024). Regardless of sex, the risk for SSE rises steeply with increasing score. Therefore, OAC initiation is currently recommended at two or more points, indicating high risk (1.5–2.2%/year), while treatment may be considered for individuals with one point at intermediate risk (0.7–1.2%/year), although evidence supporting the utility of treating borderline cases remains limited (van Doorn et al., 2017; Van Gelder et al., 2024).

The applicability of CHA_2DS_2-VASc has been questioned due to variability in SSE rates between geographical regions and other cohort specific parameters, as well as its omission of other known risk factors, resulting in a modest risk discrimination performance with a C-index of 0.61 (Lip et al., 2010; Quinn et al., 2017a; Van Gelder et al., 2024). Consequently, several other prediction models have emerged (van der Endt et al., 2022). The ATRIA score was introduced with additional considerations for renal disease and more extensive age categories. Overall, the ATRIA's C-index of 0.73 was an improvement over CHA_2DS_2-VASc, and interestingly its performance improved to 0.76 when only severe SSE were considered (Singer et al., 2013). GARFIELD-AF is a comprehensive tool integrating risk stratification for SSE, bleeding and death. The complex formula includes information on dementia and smoking status, yet the C-statistic remained 0.69 for SSE (Fox et al. 2017). In a pooled analysis, the C-statistics remained at 0.64, 0.68, and 0.71, respectively for CHA_2DS_2-VASc, ATRIA, and GARFIELD-AF, demonstrating little difference between scores (van der Endt et al., 2022). Currently, the newer scores also lack the robust validation of CHA_2DS_2-VASc; however, the additional variables may provide assurance in uncertain scenarios (Joglar et al., 2024; van der Endt et al., 2022).

To justify OAC initiation and ensure its safe use, the concomitant risks of SSE and bleeding must be carefully balanced. Many conditions, such as advanced age and hypertension, increase both risks, yet they rarely justify withholding preventive treatment, as the benefits of OAC often outweigh the risk of bleeding (Jaakkola et al., 2018; Nelson et al., 2017). Furthermore, there are very few contraindications to the use of DOACs (Van Gelder et al., 2024). Bleeding risk scores, such as the HAS-BLED, have been developed to help identify and manage modifiable risk factors (Table 2) (Joglar et al., 2024; Van Gelder et al., 2024), though validation studies have yielded mixed results in accuracy (Zeng et al., 2020; Zhu et al., 2015). Instead of recommending a specific scoring system to assess the bleeding risk, guidelines suggest strict control of comorbidities, and patient guidance in the usage of antiplatelet and anti-inflammatory drugs (Joglar et al., 2024; Van Gelder et al., 2024), as they increase major bleeding risk by approximately 50% when combined with OACs (Dalgaard et al., 2020; Fox et al., 2020).

Table 2. The HAS-BLED score for bleeding risk assessment. Modified from: (Joglar et al. 2024).

	Points
Hypertension	1
Abnormal liver and/or renal function	1 for each
Stroke history	1
Bleeding history or predisposition	1
Labile international normalized ratio	1
Elderly (age ≥ 65 years)	1
Drugs and/or alcohol concomitantly	1 for each

Risk is considered low with a score of 0, moderate with scores of 1–2, and high with a score of 3 or higher. Drugs include antiplatelet and nonsteroidal anti-inflammatory agents. Acronym HAS-BLED indicates Hypertension, Abnormal liver and/or renal function, Stroke history, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs and/or alcohol concomitantly.

2.1.3.3 Symptom management

The overall impact of AF on quality of life (QoL) is significant. Preceding the diagnosis, sudden symptoms such as palpitations, dyspnea, or fatigue are often alarming and continue to cause distress if the diagnosis remains unsure (Abu et al., 2022; J. Wang et al., 2022). To alleviate symptoms, most patients benefit from rhythm or rate control strategies aiming to either restore SR or limit tachycardia. Patient-centered decision making and frequent assessment of treatment outcomes are recommended to manage expectations of completely eliminating AF and returning to normal life (Van Gelder et al., 2024; J. Wang et al., 2022). The European guidelines recommend regularly reassessing symptom severity with an EHRA[b] classification ranging from one to four—that is, from symptom-free to disabling symptoms (Van Gelder et al., 2024).

Rate control with beta blockers is often the first approach to managing symptoms. Additionally, other agents such as calcium channel blockers or digoxin may be used to slow conduction through the atrioventricular node—thereby controlling the heart rate—if beta-blockers are contraindicated or not tolerated (Lei et al., 2018). Target heart rate should balance reducing symptoms and maintaining adequate exercise tolerance, although the RACE-II[c] trial did not observe differences in symptom severity or QoL depending on treatment intensity (Groenveld et al., 2011). Initially, guidelines recommend targeting resting heart rate < 110 beats per minute, though some patients may benefit from more stringent limits (Joglar et al., 2024; Van Gelder et al., 2024).

Rhythm control strategies aim to restore and maintain SR by antiarrhythmic drugs, CV, or ablation procedures. Even without a rapid heart rate, AF can impact QoL, especially in physically active individuals, by reducing exercise capacity (Atwood et al., 2007). Antiarrhythmic drugs (AADs) reduce AF recurrences by 20–50% but require close monitoring due to potential proarrhythmic side effects (Valembois et al., 2019). Limited response to one AAD does not exclude other drugs; however, safety should be considered in the presence of concomitant ischemic or structural heart disease as well as conduction disturbances (Crijns et al., 1991; Joglar et al., 2024; Van Gelder et al., 2024). Rhythm restoration through electrical or pharmacological CV is highly effective, with respective success rates ranging from 85% to 97%, and 49% to 94% (Kuppahally et al., 2009; Pisters et al., 2012; Tsiachris et al., 2021), and outcomes are generally better when the procedure is performed early after AF occurrence (Kuppahally et al., 2009; Nuotio et al., 2014). Without the requirement of anesthesia or fasting, pharmacological CV is a good alternative to the electrical procedure (Airaksinen, 2022), although it carries the limitations discussed with AADs. Continuous use of AADs increase the efficacy of CV and reduce recurrences later, yet up to half of patients relapse within a few months (Istratoaie et al., 2021). Ablation procedures, mostly performed via intravenous catheters, reduce the recurrence significantly, with up to 60–90% of patients remaining AF-free after one year (Calkins et al., 2009; Jaïs et al., 2008). Nevertheless, efficacy of rhythm control strategies may be improved with patient selection, since several factors such as heart failure and vascular disease affect the outcome (Jaakkola et al., 2017; Lau et al., 2017; Quiroz et al., 2024).

[b] EHRA: European Heart Rhythm Association

[c] RACE-II: Rate Control Efficacy in Permanent Atrial Fibrillation II

Compared to rate control, rhythm control strategies are often more invasive, and failed rhythm conversion attempts may in turn lead to unnecessary adverse events (Airaksinen, 2022; Latchamsetty & Morady, 2018). There is an ongoing discourse regarding clinical outcomes between rate and rhythm control strategies. Meanwhile, prioritization of symptoms and QoL has been recommended as an alternative (Olanisa et al., 2023). Restoring SR carries an increased risk for SSE by impairing the function of LAA irrespective of the method used (Grimm et al., 1993; Hansen et al., 2015); however, this is effectively countered with proper planning and OAC (Joglar et al., 2024; Van Gelder et al., 2024). Historically, the negative safety profile of AADs, developing ablation techniques, and insufficient anticoagulation may have offset the benefits of rhythm control (Calkins et al., 2009; Han et al., 2023). Recently, the EAST-AFNET 4[d] study highlighted that early rhythm control—within 1 year of AF diagnosis—lowers the risk for cardiovascular events compared to rate control (Kim et al., 2022; Kirchhof et al., 2020). The safety benefits of early rhythm control have later been verified by meta-analyses (Han et al., 2023; Hermanto et al., 2025), and while guidelines acknowledge its potential benefit, neither rhythm or rate control is recommended as the primary strategy (Joglar et al., 2024; Van Gelder et al., 2024).

2.2 Atrial cardiomyopathy

2.2.1 Overview

The atria provide a crucial contribution to normal cardiac function. In a healthy heart, they serve multiple roles: acting as both a reservoir and a contractile pump to modulate ventricular filling; facilitating electrical conduction via the sinoatrial and atrioventricular nodes; and contributing to fluid and electrolyte homeostasis through the secretion of natriuretic peptides. Any sustained pathological stimuli that disturb normal conditions may induce compensatory mechanisms, such as atrial wall thickening or chamber dilation, that have the potential to degrade into nonadaptive changes, further impacting thrombogenesis, contractility, and susceptibility to arrhythmias (Goette et al., 2016; Liu et al., 2025). Such electrical, structural, or functional changes of the atrial myocardium with the potential to cause clinically significant manifestations are the definition of aCM, according to an EHRA/HRS[e]/APHRS[f]/SOLAECE[g] consensus report (Goette et al., 2016).

[d] EAST-AFNET 4: Early Treatment of Atrial Fibrillation for Stroke Prevention Trial
[e] HRS: Heart Rhythm Society
[f] APHRS: Asian Pacific Heart Rhythm Society
[g] SOLAECE: Sociedad Latino Americana de Estimulacion Cardiaca y Electrofisiologia

The clinical importance of aCM lies in its close associations with AF and cardioembolic stroke, although much about these relationships remains unknown (Goette et al., 2016, 2024). Notably, these conditions also share common risk factors, many of which are captured by the CHA_2DS_2-VASc score (Goette et al., 2016; Ninni et al., 2024). While AF and SSE can occur in the absence of overt comorbidities, aCM is often suspected to provide the underlying substrate. Most importantly, aCM increases the risk for SSE even in the absence of AF, through various changes such as atrial fibrosis, poor contractility, and endothelial injury, which together fulfil Virchow's triad of thrombogenesis (Kreimer & Gotzmann, 2022; M. Li et al., 2022). Depending on the diagnostic method, aCM was found in 26.6–45.0% of patients with a stroke of undetermined source (Jalini et al., 2019; Ntaios et al., 2019). Despite this compelling association, results from randomized clinical trials do not support OAC treatment for patients with aCM prior to a clinical AF diagnosis (Boriani et al., 2023; Liu et al., 2025).

Although the concept of aCM has been loosely described in the literature for over 50 years (Williams et al., 1972), the consensus report was the first attempt to standardize the concept, leading to an exponential increase in pertinent publications (Goette et al., 2016, 2024). Originally, a histopathological framework for aCM categorization was suggested (Table 3) to highlight the spectrum of possible histological alterations as well as the underlying clinical conditions (Goette et al., 2016). Nevertheless, without any implications for clinical diagnosis or treatment options, the concept was poorly adopted in clinical practice (Guichard & Nattel, 2017; Liu et al., 2025). Most current research can therefore only suggest the presence of aCM rather than confirm it, as robust diagnostic criteria beyond histological assessment remain lacking (Kreimer & Gotzmann, 2022; Liu et al., 2025). Consequently, recent efforts have aimed to establish more accessible diagnostic tools, while also exploring the underlying pathogenesis and clinical importance of aCM (Goette et al., 2024; M. Li et al., 2022; Liu et al., 2025).

Table 3. Histological classification of atrial cardiomyopathy. Modified from: (Goette et al. 2016).

	Histological characterization	Potential causes
Class I	Primarily cardiomyocyte dependent changes involving hypertrophy and myocytolysis; no significant fibrosis or other interstitial alterations	- Atrial fibrillation - Hypertension
Class II	Primarily fibrotic alterations with normal cardiomyocyte appearance	- Aging - Smoking
Class III	Combination of cardiomyocyte changes and fibrotic alterations	- Heart failure - Valvular disease
Class IV	Extracellular matrix alterations involving amyloid deposit, fatty infiltrate, inflammatory cells, or other non-fibrotic changes	- Amyloidosis - Obesity

Various histological properties in the atrial myocardium indicate atrial cardiomyopathy. Patients may shift between classes over time, but the system does not depict a linear progression from Class I to Class IV.

2.2.2 Pathogenesis

Atrial remodeling refers to the adaptive process of cardiac tissue eventually manifesting aCM (Liu et al., 2025; D. Qiu et al., 2021). The electrical, structural, and functional alterations accumulate over time and may be caused by sustained arrhythmias and other cardiac or extracardiac conditions that introduce volume or pressure overload, ischemia, or inflammation to the atria (Dmour et al., 2021; Goette et al., 2016; D. Qiu et al., 2021). Although several critical structures, including the sinoatrial and atrioventricular nodes, are located in the right atrium, changes in the LA are typically of greater clinical interest due to its increased susceptibility to external stressors and its notable contribution to cardiac function. Early stages of remodeling manifest electrically as reversible ion-channel abnormalities, whereas structural alterations entailing cardiomyocyte hypertrophy and interstitial fibrosis occur later and are often irreversible (Goette et al., 2016; D. Qiu et al., 2021).

2.2.2.1 Electrical remodeling

The term *electrical remodeling* was first introduced three decades ago to describe the shortening of atrial action potential duration and refractory period in an animal model with device-induced AF (Wijffels et al., 1995). Simultaneously, another animal experiment reported similar findings, with both studies showing that sustained high-rate pacing prolonged the duration of AF episodes (Morillo et al., 1995; Wijffels et al., 1995). In humans, the shortening of action potential duration was even more pronounced, and it occurred quicker (Daoud et al., 1996; Franz et al., 1997). Notably, all the induced changes and the rhythm spontaneously normalized over time (Pandozi et al., 1998; Wijffels et al., 1995). The intracellular mechanisms underlying these changes are complex but are predominantly driven by a decrease in calcium-ion currents and a subsequent increase in potassium-ion currents, secondary to alterations in ion-channel activation and gene expression (Martins et al., 2014; Shen et al., 2019). Furthermore, tachyarrhythmias and abnormal pressure conditions alter the distribution and orientation of gap junctions by disrupting the expression and localization of key proteins, including connexin 40 and connexin 43 (Shen et al., 2019). Gap junctions are essential for mediating electrical impulses between cardiomyocytes (Lo, 2000), and consequently, abnormalities in connexin expression can reduce atrial conduction velocity and alter conduction patterns (Dhein & Salameh, 2021; Medi et al., 2011). In chronic cardiovascular diseases, arrhythmogenesis is promoted by remodeling of the autonomic nervous system (Shen et al., 2019). Sympathetic nerve sprouting and hyperinnervation of cardiomyocytes enhance calcium-dependent cardiac activity and promote the occurrence of delayed afterdepolarizations (P. S. Chen et al., 2014; Iwasaki et al., 2011), while parasympathetic hyperactivity shortens the action potential and refractory period, facilitating signal reentry (Arora et al., 2007; Kharbanda et al., 2022).

2.2.2.2 Structural remodeling

Structural remodeling involves alterations in cellular composition and extracellular matrix (ECM) architecture at the microscopic level, which may contribute to macroscopic manifestations such as atrial dilation (Y. C. Chen et al., 2024; D. Qiu et al., 2021). These modifications primarily arise in response to atrial pressure overload and prolonged tachycardia, and are mediated by oxidative stress, inflammation, and calcium overload (Casaclang-Verzosa et al., 2008; D. Qiu et al., 2021; Shen et al., 2019). Cardiomyocytes respond to tachycardia-induced stressors with myocytolysis—the loss of contractile sarcomeres—in order to conserve energy. In contrast, increased atrial wall stretching and reduced coronary blood flow promote a transition from fast to slow sarcomere proteins, making cardiomyocytes more ischemia-resistant at the expense of contraction velocity (Casaclang-Verzosa et al., 2008; Corradi, 2014). Sustained stress may turn these protective alterations maladaptive, ultimately leading to cell death (Shen et al., 2019).

Fibrosis, characterized by excess collagen deposition by myofibroblasts, may occur as a reparative process after cardiomyocyte loss, or as a reaction to external stressors (Kong et al., 2013; Ma et al., 2021; D. Qiu et al., 2021). The type of sustained damage influences the composition of proteins deposited into the ECM, affecting both the tissue's tensile strength and cellular signaling. Activated myofibroblasts also produce proteolytic enzymes, such as matrix metalloproteinases and their inhibitors, which, if dysregulated, can increase myocardial stiffness, promote cardiomyocyte apoptosis, and activate other fibrogenic mediators (Frangogiannis, 2019). Interaction with cardiomyocytes alters their electrical features, while excess fibrosis disturbs cell-to-cell continuity, causing further conduction disturbances (Frangogiannis, 2019; Ma et al., 2021). The effect is more pronounced when organized conductive pathways, such as the interatrial Bachmann's bundle, are affected, leading to desynchronized contractions between the atria (Becker, 2004; Bejarano-Arosemena & Martínez-Sellés, 2023).

2.2.2.3 Functional remodeling

Functional remodeling encompasses changes in cellular metabolism and hormonal regulation. With the heightened energetic demand, caused by increased activity, cardiomyocytes adapt by making a shift from fatty-acid metabolism towards glucose-based energy expenditure. However, suboptimal glucose oxidation and consequent energy starvation impair ion-channel activity, leading to contractile failure (Casaclang-Verzosa et al., 2008; D. Qiu et al., 2021). In order to decrease atrial filling pressure and wall stretch, cardiomyocytes increase the secretion of natriuretic peptides, which lower systemic blood pressure and attenuate myofibroblast collagen synthesis (Casaclang-Verzosa et al., 2008; Dietz, 2005). The levels of circulating atrial natriuretic peptides (ANPs) appear to negatively correlate with the extent of atrial fibrosis (Yoshihara et al., 2002), suggesting that the response is limited to preventing atrial remodeling (Casaclang-Verzosa et al., 2008). Atrial stretch hyperstimulates the local renin–angiotensin–aldosterone pathways in cardiomyocytes, fibroblasts, and endothelial cells, promoting fibrosis and prothrombotic factors such as endothelial dysfunction, vasoconstriction, and platelet reactivity. Under normal conditions, this pathway regulates ECM composition, as well as cardiomyocyte size and contractility (De Mello, 2011; Frangogiannis, 2019).

The remodeling mechanisms occur concurrently, each reinforcing the other (D. Qiu et al., 2021). Slow electrical conduction in the enlarged atria, accompanied by fibrosis and altered cardiomyocytes, leads to poor contractility and blood stasis (M. Li et al., 2022). While the physiological basis for these alterations is to adapt and protect the tissues, sustained insult can result in irreparable damage (Casaclang-Verzosa et al., 2008; D. Qiu et al., 2021). For example, at first, atrial dilation serves to counteract increased pressure conditions, but the advantage is lost with fibrotic stiffness (Goette et al., 2024). Ultimately, the remodeled atria may support self-propagating electrical activity that persists within the heterogeneously altered tissue, leading to uncoordinated contractions and possibly AF (Shen et al., 2019).

2.2.3 Diagnostic methods

2.2.3.1 Electrocardiography

The conventional 12-lead ECG allows for noninvasive evaluation of cardiac conduction direction, velocity, and signal amplitude, which reflect the electroanatomic framework. More specifically, abnormalities in the P-wave may indicate disturbances in atrial activation. In normal SR, the sinoatrial node initiates an inferiorly propagating impulse that first depolarizes the right atrium, with subsequent activation of the LA mainly through the interatrial Bachmann bundle (Baranchuk & Bayés de Luna, 2015; Platonov, 2008). In the ECG, this pattern of depolarization produces the typical P-wave, which in most leads appears as a symmetrical dome-shaped waveform with a duration of less than 120 ms (Baranchuk & Bayés de Luna, 2015). Several variations have been indirectly associated with aCM based on findings from imaging, electroanatomical mapping (EAM), or histology (Goette et al., 2024; Liu et al., 2025).

Increased P-wave duration indicates reduced conduction velocity throughout the atria and has been linked to LA enlargement, contractile dysfunction, fibrosis, and low-voltage areas in EAM (Bayés De Luna et al., 2012; L. Y. Chen et al., 2022; Huo et al., 2014; Müller-Edenborn et al., 2022). The 120 ms cut-off for normal P-wave duration has been widely adopted, yet a standardized reference value distinguishing normal from abnormal atrial substrate remains undefined (Magnani et al., 2009).

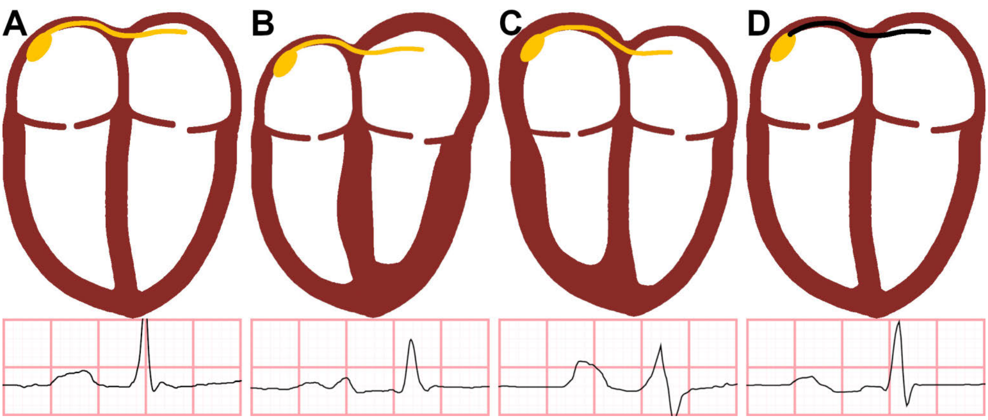

Figure 3. A simplified schematic illustration of the heart and its interatrial conduction system under various conditions, accompanied by corresponding electrocardiogram examples. The yellow oval represents the sinoatrial node, which initiates the electrical impulse, and the yellow curve denotes the interatrial Bachmann bundle.
A: Normal conduction.
B: Left atrial enlargement.
C: Right atrial enlargement.
D. Interatrial conduction defect.

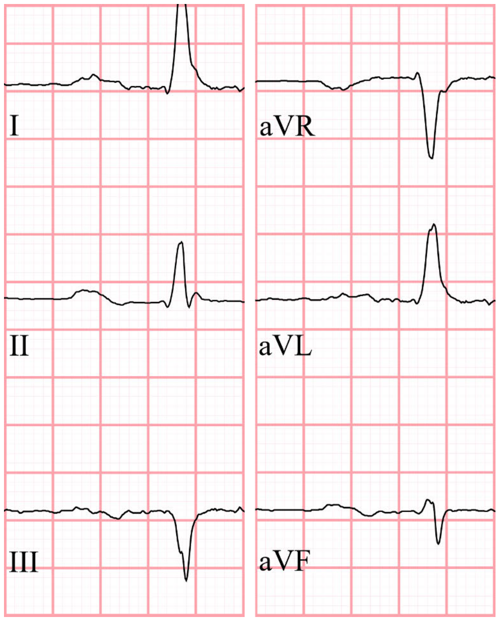

Figure 4. An example electrocardiogram showing advanced interatrial block. The P-wave duration is 125 ms and exhibits a biphasic morphology in the inferior leads (II, III, and aVF).

Additionally, heterogeneous atrial substrate may produce variable conduction velocities across the atria, resulting in different P-wave durations from beat to beat (Alexander et al., 2021). This variation can be quantified as P-wave dispersion, obtained by subtracting the shortest P-wave duration from the longest (Okutucu et al., 2016).

Assessing the P-wave morphology in addition to duration may provide more detailed information on atrial enlargement and conduction disturbances (Figure 3). A tall, single-peaked P-wave in the inferior limb leads may be observed in pulmonary disease and is indicative of right atrial dilation, although the clinical associations are weak (Hancock et al., 2009; Harrigan & Jones, 2002). Conversely, a P-wave with two distinct domes or a small notch typically reflects LA enlargement and left sided conduction delay (Edhouse et al., 2002; Hancock et al., 2009). In addition to the maximum voltage, the initial part of the P-wave shows only little variation in morphology due to the location of the sinoatrial node, whereas the direction of depolarization in the LA is significantly more variable owing to the complex interatrial conduction pathways (L. Y. Chen et al., 2022). Notably, an impairment in the interatrial Bachmann's bundle redirects electrical conduction posteriorly through the LA leading to a biphasic (positive–negative) P-wave in the inferior leads (Bayés De Luna et al., 2012). This phenomenon, known as advanced interatrial block (AIAB), is also associated with prolonged refractory periods and an increased occurrence of premature atrial contractions, both of which facilitate signal re-entry (Bayés De Luna et al., 2012; Power et al., 2022). An example of AIAB is presented in Figure 4.

In lead V1, the P-wave is typically biphasic, with the latter negative deflection representing LA activation; the product of its amplitude and duration defines the P-terminal force (PTF). A PTF greater than 40 mm·ms was initially proposed as a marker of LA enlargement, but more recent studies have shown that the terminal duration correlates with atrial fibrosis, while the terminal amplitude reflects LA strain (Lebek et al., 2021; Liu et al., 2025; Win et al., 2014).

P-wave assessment is limited to patients in SR, because in AF, the chaotic atrial activation produces only a fibrillating baseline without distinguishable P-waves. In theory, the F-wave amplitude reflects viable atrial tissue and the degree of organized conduction (Peter et al., 1966). However, the measurement lacks standardization, and it is unknown whether the amplitude remains stable across separate ECG recordings. While this topic remains largely unexplored, some studies have associated low-amplitude F-waves with LA enlargement and low LAA flow velocity (İçen et al., 2020; Kawaji et al., 2022).

Despite growing evidence supporting associations between ECG parameters and aCM the current knowledge relies mainly on indirect correlations, such as imaging, rather than histopathological validation. Additional studies are warranted to determine how progressive atrial remodeling influences P-wave parameters, which is essential for establishing the utility of ECG in diagnosing aCM.

2.2.3.2 Electrophysiology

EAM is an invasive procedure, often performed in conjunction with catheter ablation, that combines structural anatomy with information on atrial voltage, activation sequence, and conduction velocity (Goette et al., 2024). The extent of low-voltage areas in EAM seems to correlate well with fibrosis, and the histopathological changes become more pronounced with lower voltages (Goette et al., 2024; Schaeffer et al., 2019). Recently, Takahashi et al. demonstrated that other pathological changes, such as sarcomere loss, are also associated with voltage reduction, in addition to fibrosis (Takahashi et al., 2023). Although studies have shown consistent results, voltage readings can be distorted by increased atrial pressure, varying tissue thickness, or even prevailing heart rhythm (Kariki et al., 2023; Liu et al., 2025). Importantly, as an invasive procedure, EAM cannot be the primary method for prognostic evaluation (M. Li et al., 2022).

2.2.3.3 Imaging

Different imaging modalities provide insight into the structural, functional, and metabolic conditions of the atria (Kreimer & Gotzmann, 2022). Due to its widespread availability, echocardiography is usually the primary technique in assessing aCM-related changes (Boriani et al., 2023; Liu et al., 2025). Studies have used LA diameter as a marker for aCM, although this method is less accurate at detecting dilation than volumetric assessments, due to the complex, asymmetrical geometry of the atrium and the heterogeneity of remodeling (Kariki et al., 2023; Liu et al., 2025). Recent evidence suggests that the smallest LA volume—measured at the end of ventricular diastole—could be a better indicator of atrial dysfunction compared to conventionally used maximum volume measurement (Thomas et al., 2020). Furthermore, due to its correlation with poorly conducting areas in EAM and the extent of myocardial fibrosis (Eichenlaub et al., 2021; Her et al., 2012; Kuppahally et al., 2010), LA strain measurement using speckle-tracking echocardiography has been proposed as a potential indicator for aCM (Kreimer & Gotzmann, 2022; Liu et al., 2025),

Magnetic resonance imaging (MRI) is the gold standard for measuring cardiac structures and function, providing better accuracy and reproducibility over echocardiography (Boriani et al., 2023; Liu et al., 2025). Late gadolinium enhancement MRI allows for the detection of fibrosis in the atria with a high correlation with histological samples (Bouazizi et al., 2018), but is limited by low image resolution due to the thin atrial wall (Goette et al., 2024; Kreimer & Gotzmann, 2022). Currently, the technology appears more suited to detecting isolated fibrotic regions than diffuse fibrosis (Flett et al., 2010; Goette et al., 2024).

Computed tomography (CT) offers accurate atrial volumetric assessment and has recently been utilized for evaluating atrial strain, with results comparable to speckle-tracking echocardiography. Positron emission tomography–CT (PET-CT) presents a potential tool in detecting increased atrial metabolic activity by tracking 18F-fluorodeoxyglucose uptake (Kreimer & Gotzmann, 2022). Although studies on aCM are scarce, Watanabe et al. demonstrated that PET-CT can differentiate between persistent and paroxysmal AF patients (Watanabe et al., 2019).

2.2.3.4 Biomarkers

Several blood-based biomarkers of cardiac injury, inflammation, and fibrosis have been observed to mark atrial remodeling or aCM, although they may not be entirely atria-specific molecules (Kreimer & Gotzmann, 2022; Liu et al., 2025). Furthermore, biomarker secretion can vary diurnally and is influenced by factors such as concomitant AF, chronic cardiovascular diseases, and body mass index, complicating the evaluation of their reliability as diagnostic or prognostic markers

(Goette et al., 2024; M. Li et al., 2022; Pouru et al., 2020). Natriuretic peptides secreted in response to pressure overload appear to correlate with LA enlargement, with ANP showing a stronger correlation compared to brain natriuretic peptide (BNP), which is produced in both the atria and ventricles (Kreimer & Gotzmann, 2022; Liu et al., 2025). Additionally, BNP has been associated with echocardiographic LA remodeling and dysfunction (Sieweke et al., 2020).

While inflammation is a key promoter of atrial remodeling, most inflammatory markers, such as interleukin-6 and high-sensitivity C-reactive protein, tend to increase in the presence of AF, rather than specifically reflecting underlying aCM (Kreimer & Gotzmann, 2022; Stanciu et al., 2018). Transforming growth factor ß1, an anti-inflammatory cytokine that also promotes fibrosis, has been associated with low-voltage areas and LA volume (Heinzmann et al., 2018; Stanciu et al., 2018). Among other cells, cardiomyocytes and fibroblasts increase the expression of galectin-3 and the soluble suppression of tumorigenicity 2 in response to mechanical stress and inflammation. Galectin-3 promotes fibroblast activation and collagen deposition and is associated with atrial fibrosis detected by late gadolinium enhancement MRI, as well as low-voltage areas identified in EAM (Aksan et al., 2022; Procyk et al., 2023). Soluble suppression of tumorigenicity 2 inhibits the anti-fibrotic effects of interleukin-33 by acting as a decoy receptor, and elevated levels of it have been associated with atrial low-voltage areas (P. Chen et al., 2023; Fan et al., 2022).

2.2.4 Clinical importance

AF and aCM appear closely related, although the causal relationship remains unclear. In theory, aCM provides the framework for the initiation, maintenance, and progression of AF; however, the reverse is also true, as AF itself can trigger remodeling (Goette et al., 2016). While in normal SR, electrical activation travels homogenously through the atria from right to left, controlled by regular impulses from the sinoatrial node, AF is propagated by rapid ectopic impulses which require a heterogeneously remodeled atrial substrate to sustain the arrhythmia. Ectopic firing, typically originating from the pulmonary vein area, is facilitated by changes in cardiomyocyte action potentials and refractory periods, while altered conduction velocity promotes re-entry, allowing the activity to persist (Iwamiya et al., 2024; Wijesurendra & Casadei, 2019). These electrophysiological and structural changes not only maintain AF but are further reinforced by its ongoing presence—thus, AF begets AF (Wijesurendra & Casadei, 2019; Wijffels et al., 1995). Despite this interplay, notable discrepancies exist between the rate at which these alterations develop and their clinical manifestations: patients with severe fibrosis may present with paroxysmal rather than persistent AF, and fibrosis may develop even in the absence of AF (Kottkamp, 2012; Kreimer & Gotzmann, 2022).

The proarrhythmogenic atrial substrate in aCM may also influence the effectiveness of rhythm control strategies. Time spent in AF plays a critical role in determining the success of interventions, with longer durations associated with reduced efficacy (Airaksinen, 2022). In the FinCV studies, acute CV performed within 48 hours of AF onset was successful in 94.5% of cases, while elective procedures restored SR in 84.8% of cases (Grönberg et al., 2015; Hellman et al., 2017). Similarly, the rate of AF recurrence may reduce in the long term with repeat CVs (Voskoboinik et al., 2019). Meanwhile, patients expressing markers of aCM, such as LA enlargement or impaired interatrial conduction, are at increased risk for recurrent AF after CV (Ecker et al., 2018; Fujimoto et al., 2018). The efficacy of catheter ablation is equally affected by the duration of AF and concomitant aCM (Karanikola et al., 2025), but a successful procedure appears to reduce LA size and improve atrial conduction velocity (Goette et al., 2024). Additionally, the EAST-AFNET 4 trial observed a reduction in AF-related adverse events when a rhythm control approach was chosen within one year of first AF diagnosis, suggesting a correlation with AF burden and SSE incidence (Alkhouli & Friedman, 2019; Kirchhof et al., 2020). A striking discovery, supported by later studies and meta-analyses, is that the comprehensive management offered to patients could, in fact, be treating the underlying atrial substrate, not only the rhythm, thus reducing morbidity (M. Li et al., 2022; Liu et al., 2025).

Beyond its impact on AF burden, the presence of aCM further predisposes AF patients to SSE, among other adverse outcomes (Goette et al., 2016). In MRI studies, patients with AF and a history of SSE exhibited more extensive atrial fibrosis (Daccarett et al., 2011), and conversely, those with severe atrial fibrosis had nearly a fourfold increased risk of stroke (King et al., 2017). Similarly, LA enlargement was associated with a 1.7-fold increased risk of SSE, and a 1.6-fold increased risk of recurrent SSE, even after adjusting for other risk factors and OAC therapy (Hamatani et al., 2016; Ogata et al., 2017). Blood biomarkers and ECG abnormalities indicative of underlying aCM have demonstrated comparable effects (Alkhouli & Friedman, 2019). The increased susceptibility for SSE brought by aCM could explain some of the heterogeneity observed in the performance of current risk prediction models, such as the CHA_2DS_2-VASc score (Alkhouli & Friedman, 2019; Quinn et al., 2017). Incorporating aCM-related observations into existing risk scores has been shown to improve predictive accuracy and may therefore help identify otherwise low-risk patients who could benefit from OAC (Alkhouli & Friedman, 2019; Liu et al., 2025). Nevertheless, it remains unclear how to best incorporate this information into clinical practice (Joglar et al., 2024; Van Gelder et al., 2024).

Current guidelines and recommendations lack information about the optimal management of AF with concomitant aCM (Goette et al., 2024; Van Gelder et al., 2024). Essentially, effective treatment of comorbidities, as suggested by the AF-CARE pathway, may partially reverse aCM-related alterations and help maintain SR, while also being beneficial for the risk of SSE (Liu et al., 2025; Van Gelder et al., 2024).

2.3 Personalized risk assessment with 12-lead electrocardiogram

2.3.1 Overview

The ECG is a noninvasive, low-cost, and widely accessible test that can be utilized without special training. In clinical practice, its applications are often limited to diagnosing arrhythmias, ischemia, or structural heart disease, leaving atrial pathologies underrecognized (L. Y. Chen & Soliman, 2019). In response to this gap, recent efforts have focused on establishing correlations between clinical end points and various P-wave parameters (L. Y. Chen & Soliman, 2019; Goette et al., 2024). Alterations in the atrial substrate affect conduction velocity, signal amplitude, and contraction sequence, which can be evaluated on the ECG through the assessment of P-wave duration and morphology (Goette et al., 2024). P-wave elongation of over 120 ms, AIAB, and PTF over 40 mm·ms are among the most studied atrial abnormalities, collectively addressing all aspects of substrate alteration (Goette et al., 2024; Kreimer & Gotzmann, 2022). Building on this, studies continue to investigate the utility of revised cut-off values, such as P-wave duration exceeding 150 ms or 180 ms, in improving diagnostic discrimination and predictive accuracy (Müller-Edenborn et al., 2022).

Several novel P-wave indices have emerged, but they either require extra calculation or have overlap with established parameters (Liu et al., 2025). For example, the morphology–voltage–P-wave duration (MVP) score incorporates P-wave voltage in lead I into a model with P-wave duration and AIAB (Alexander et al., 2019). While both lead I voltage and PTF are indicative of viable myocardium in the LA, PTF was excluded due to its association with LA enlargement, although recent evidence suggests otherwise (Alexander et al., 2019; Lebek et al., 2021). Furthermore, P-wave axis in the orthogonal leads—often automatically reported on the ECG printout—reflects the net direction of atrial conduction but is also influenced by the anatomical positioning of the heart within the thoracic cavity (Alexander et al., 2021; German et al., 2016). Additionally, the calculation of P-wave axis is limited by gross conduction disorders, such as AIAB (L. Y. Chen et al., 2022). Due to obvious cross-correlations between parameters, most studies focus on assessing the predictive power of few select indices, instead of the ECG as a whole. Nevertheless, with increasing evidence, ECG parameters reflecting underlying aCM have been associated with new-onset AF, AF recurrence, and SSE, although additional work is required to ensure clinical applicability (L. Y. Chen & Soliman, 2019; Goette et al., 2024).

2.3.2 Atrial fibrillation

2.3.2.1 Prediction of new-onset atrial fibrillation

The conventional 12-lead ECG remains the gold standard for diagnosing AF. During AF arrhythmia, chaotic atrial activity appears as a fibrillatory baseline instead of regular atrial P-waves, and the normal pattern of ventricular contractions becomes irregular. While the clinical presentation is straightforward, the episode often subsides by the time of ECG recording, complicating diagnosis (Joglar et al., 2024; Van Gelder et al., 2024). Nevertheless, even in the absence of active arrhythmia, certain P-wave characteristics may indicate underlying aCM and help identify patients at increased risk of developing AF (Alexander et al., 2021; Chousou et al., 2023).

Patients with new-onset AF often present with longer P-waves and AIAB (Alexander et al., 2021; L. Y. Chen & Soliman, 2019; Chousou et al., 2023). P-wave duration over 120 ms is associated with 1.4–1.9-fold increase in AF risk, and this relationship seems dose-dependent (Istolahti et al., 2020; J. B. Nielsen et al., 2015; Soliman et al., 2009). In patients with heart failure, extremely long P-waves (> 150 ms) increased AF risk by nearly tenfold (Müller-Edenborn, Minners, et al., 2020). By incorporating abnormal biphasic morphology with an elongated P-wave, AIAB appears to be a more robust predictor of new AF, with a meta-analysis demonstrating a 3.9-times-greater risk (Zagoridis et al., 2023). Furthermore, the MVP risk score provided additional benefit in AF prediction after coronary angiography by adding P-wave voltage into a model with P-wave duration and AIAB (Alexander et al., 2019). Evidence of the usability of the MVP-score in the general population is limited. Although a Swedish epidemiological study showed a more than sixfold increase in AF risk with elevated MVP scores, the study was underpowered due to the small number of new AF cases and a narrow score distribution (Baturova et al., 2024).

Meanwhile, the role of PTF in identifying patients at risk of developing AF appears questionable due to discrepancies in cut-off values and study populations. A meta-analysis associated PTF with an overall 40% increase in odds of developing AF; however, the odds were only 20% larger when healthy populations were considered (Huang et al., 2020). Among the referenced studies with healthy populations, comparisons were performed using either the established cut-off value of 40 mm·ms (Eranti et al., 2014; Lehtonen et al., 2017; Magnani et al., 2014; Rasmussen et al., 2020), or lowest and highest 5% percentiles (Soliman et al., 2009). Only the study by Magnani et al. demonstrated a statistically significant hazard ratio (HR) of 1.6 with the conventional cut-off value (Magnani et al., 2014). Meanwhile, PTF as a continuous variable performed consistently, and higher cut-off values were stronger indicators for new AF (Eranti et al., 2014; Huang et al., 2020).

According to meta-analysis of 11 studies, a P-wave axis outside the normal range 0–75◦ doubles the risk for new AF (Chattopadhyay et al., 2022). Nevertheless, the utility remains unsure, as referenced studies did not adjust the multivariable models with any known morphological P-wave factors. As a relatively new marker, the predictive value of P-wave dispersion has primarily been investigated in studies with limited sample sizes or in populations with comorbidities that predispose to cardiac issues (Chousou et al., 2023). In a healthy cohort of over 40,000 patients, P-wave dispersion greater than 80 ms nearly doubled the risk of incident AF, although the association was no longer significant after multivariable adjustment (Perez et al., 2009).

In summary, multiple P-wave parameters—such as prolonged duration, biphasic morphology, and axis deviation—are associated with elevated risk of developing AF. While some markers show strong predictive value, the clinical utility of others remains uncertain due to inconsistent findings across populations and variability in cut-off values used.

2.3.2.2 Prediction of atrial fibrillation recurrence

After the initial AF diagnosis, ECG may be further utilized in determining suitable management strategies (Potpara et al., 2021). Patients with abnormal P-waves may be prone to early AF recurrence after rhythm control attempts; however, data on CV outcomes are mostly limited to small-scale studies and varying follow-up durations (Alexander et al., 2021; L. Y. Chen & Soliman, 2019). P-wave duration over 142 ms increased the odds of AF recurring one month after CV threefold (Gonna et al., 2014), while a cut-off at 135 ms demonstrated a 1.6-fold increase in odds at 2 months (Raitt et al., 2006). AIAB was a significant predictor of post-CV AF recurrence, with a fourfold increase in risk at one month. Additionally, P-wave dispersion increased the risk by 6% per millisecond (Fujimoto et al., 2018). Studies reporting the association of P-wave parameters with the immediate success of CV are limited.

With catheter ablation being an invasive procedure, patient selection becomes increasingly important. In a study by Müller-Edenborn et al., abnormal P-wave duration and morphology—reflected in the degree of atrial low-voltage substrate—correlated with AF recurrence within one year after catheter ablation. While 77% of patients with a P-wave duration of less than 150 ms retained SR at one year, only 33% of those with a P-wave duration of over 180 ms or AIAB morphology were in SR, corresponding to more than a fourfold increase in risk of recurrence (Müller-Edenborn, Chen, et al., 2020). These results were consistent with a meta-analysis reporting P-wave duration cut-offs of 120 ms, 140 ms, and 150 ms increasing the odds of recurrence by 2-fold, 2.4-fold, and 10.9-fold, respectively. Additionally, patients with AIAB were four times more likely to have recurrent AF. However, the 22 studies included in the analysis reported highly variable follow-up durations, ranging from only 3 to 50 months, introducing substantial heterogeneity across the findings (Intzes et al., 2023). Meanwhile, in a study of 207 patients, each point in the six-point MVP score was shown to nearly triple the risk of 12-month recurrence (Yang et al., 2020).

The applicability of PTF in predicting post-ablation AF recurrence has received little attention, with mixed results. With a cut-off of 40 mm·ms, Wang et al. reported a 2.3-fold increase in the risk of recurrent AF over an average follow-up period of two years—while, when treated as a continuous variable, each 10 mm·ms increment was associated with a 22% increase in risk (Z. Wang et al., 2024). Another study demonstrated that PTF over 40 mm·ms, measured 3 months after ablation, doubled the risk of AF recurrence during a three-year follow-up (Sudo et al. 2023). Conversely, using the same PTF cut-off value, Qiu et al. found no difference in recurrence rates during a three-year follow-up period after ablation (Y. Qiu et al., 2024).

The scope of ECG appears to extend beyond AF diagnosis to identifying individuals at risk of developing AF and those who may not benefit from rhythm control (Guo et al., 2023). Still, further research is required to establish uniform reference values for continuous variables, and to evaluate the performance of several markers simultaneously (Chousou et al., 2023), as was demonstrated with the MVP score (Alexander et al., 2019).

2.3.3 Stroke or systemic embolism

Enhancing SSE prediction beyond the CHA_2DS_2-VA score could help optimize OAC treatment in AF patients, particularly in borderline cases (L. Y. Chen & Soliman, 2019). While the characteristics of the arrhythmia itself—such as episode duration or frequency—are clinically relevant, it remains unclear how much AF burden warrants initiation of OAC (Joglar et al., 2024; Van Gelder et al., 2024). Moreover, the potential of ECG has been recognized as an additional risk factor (L. Y. Chen & Soliman, 2019; Liu et al., 2025). In an attempt to integrate abnormal P-wave axis into the CHA_2DS_2-VASc score, only a modest improvement from 0.60 to 0.67 was observed in the predictive C-statistic (Maheshwari et al., 2019).

Nevertheless, several studies have consolidated the additional value of P-wave analysis in SSE risk assessment (L. Y. Chen & Soliman, 2019).

The utility of the ECG in predicting SSE incidence has been best shown in AF-naïve patients (Prasitlumkum et al., 2020). While several studies simultaneously reported AF incidence and adjusted risk calculations accordingly, it is possible that asymptomatic or paroxysmal AF cases were missed (Kamel et al., 2014; Maheshwari et al., 2019; J. B. Nielsen et al., 2015). While a large Danish population study demonstrated a 12% increase in SSE risk with P-wave duration exceeding 130 ms (J. B. Nielsen et al., 2015), the conventional cut-off of 120 ms was not significant in a meta-analysis (Prasitlumkum et al., 2020). Instead, the presence of AIAB nearly doubled the risk of SSE (Prasitlumkum et al., 2020). PTF values exceeding 40 mm·ms are associated with a 1.3–2.1-fold increased risk (Kamel et al., 2014; Okin et al., 2016), while as a continuous variable, the risk increases by 21% for each standard deviation (Kamel et al. 2015). In patients with PTF more than 50 mm·ms, the risk of recurrent stroke was 1.6-fold greater compared to those without, regardless of OAC treatment (Wu et al., 2022). Additionally, AIAB, PTF, and abnormal P-wave axis were found two to three times more common in patients with embolic strokes compared to those with non-embolic strokes (Iwakawa et al., 2022; Stalikas et al., 2022).

Limited research has explored the role of ECG in predicting SSE risk in the context of existing AF. In SR recordings, each 10 mm·ms increment in PTF increased the odds of SSE 1.2-fold in AF patients (Inoue et al. 2018). Instead, the F-wave amplitude in AF ECGs has received more attention, though with mixed results. A fine F-wave, defined as a maximum amplitude of less than 0.5 mm, was associated with more than double the risk of SSE in a study consisting of over 700 non-anticoagulated AF patients (Relander et al., 2024). These findings were consistent with an earlier study of 82 patients, which reported a threefold increase in odds when F-wave amplitudes were 1 mm or less (Nakagawa et al., 2001). In contrast, coarse F-waves, with amplitudes of 1 mm or greater, were associated with a fourfold increase in the odds of SSE in a study of 100 AF patients with rheumatic mitral stenosis (Mutlu et al., 2003).

Given accumulating evidence that ECG parameters can predict new-onset AF, as well as SSE risk in both AF and non-AF patients, there is growing interest in exploring the feasibility of initiating OAC treatment for patients with ECG-indicated aCM (Power et al., 2022). In the recent ARCADIA[h] trial, investigating the efficacy of a DOAC compared to aspirin in the secondary prevention of stroke in AF-naïve

[h] ARCADIA: Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke

patients with markers of aCM, no significant difference was observed between the two treatments. While the diagnosis of aCM was based on either abnormal PTF, elevated pro-BNP, or enlarged LA, none of these individual criteria showed evidence of DOAC efficacy in subgroup analyses (Kamel et al., 2024). Furthermore, additional research is needed to assess whether AF patients with otherwise low risk for SSE might benefit from OAC based on P-wave characteristics (Guo et al., 2023; Power et al., 2022).

To sum up, P-wave parameters have shown potential in predicting SSE, particularly in AF-naïve patients, though their added value beyond conventional risk models remains modest. Ongoing research is evaluating whether these markers could guide OAC initiation in low-risk or AF-free individuals; however, recent trials have yet to show clear benefit.

2.3.4 Dynamic nature of the electrocardiogram

In addition to demonstrating clinical relevance and pathophysiological validity, the real-world applicability of P-wave parameters depends on achieving measurement repeatability, establishing standardized reference values, and ensuring long-term stability of the observed abnormalities (L. Y. Chen & Soliman, 2019; Magnani et al., 2009; Soliman et al., 2009). Since the introduction of the ECG, measurement accuracy has improved significantly with the transition from paper recordings to electronic tracings (Magnani et al., 2009). Both intraobserver and interobserver errors in measuring P-wave duration were reduced by half with digital methods compared to paper (Andrikopoulos et al., 2000). Recent advances with signal-averaged ECG and artificial intelligence aim to further reduce artifacts and streamline the process (L. Y. Chen & Soliman, 2019).

Commonly used reference values, such as 120 ms for prolonged P-wave duration, are often derived from healthy cohorts and come with a high prevalence, hindering clinical utility (Magnani et al., 2009, 2010; Soliman et al., 2013). This stands in contrast to the growing body of evidence indicating that alternative cut-off points are associated with meaningful outcomes (Müller-Edenborn, Minners, et al., 2020, Eranti et al. 2014). There are also inconsistencies in the application of P-wave parameters (L. Y. Chen & Soliman, 2019). While in the consensus report by Bayés De Luna et al., AIAB was defined as biphasic P-waves in all inferior ECG leads (II, III, and aVF) in addition to elongated P-wave, studies often allow the diagnosis with two out of three biphasic waves (Istolahti et al., 2022; O’Neal et al., 2016). It also matters whether studies evaluate the mean or maximum values of measurements, as with artifacts or marked P-wave dispersion may shift patient categorization from normal to pathological (Magnani et al., 2014).

Robust, longitudinal studies assessing the evolution of P-wave parameters over time are scarce (Chousou et al. 2023). While the incidence of abnormalities have been mainly associated with aging and chronic cardiovascular conditions, treating the underlying risk factors may also improve the ECG (Aizawa et al., 2019; Istolahti et al., 2022; Lehtonen et al., 2017). Aggressive treatment of hypertension or significant weight loss lower atrial pressure and may thereby reduce P-wave duration, although the effect is modest and does not normalize values to those of healthy controls (Aizawa et al. 2019; Duru et al. 2006). Similarly, minor improvement was observed in P-wave duration and AIAB in patients with cardiac resynchronization therapy (Alexander et al., 2017). In a Finnish population study of over 6.000 patients, P-wave duration, AIAB, and PTF—when treated as categorical variables—were found to be labile over a follow-up period of 11 years. However, some of the observed improvements and progressions may have been attributable to borderline baseline measurements, and it is likely that some of the patients with the most severe abnormalities did not survive the duration of follow-up (Istolahti et al., 2022). Meanwhile, in an observational study involving 67 participants, no significant changes in P-wave duration or morphology were detected over a 3-year period (Havmöller et al., 2009).

Although certain features of the P-wave show promise in identifying patients at risk for AF and SSE, further research on the evolution of these parameters is needed before they can be reliably used to guide treatment decisions (L. Y. Chen & Soliman, 2019; Chousou et al., 2023).

3 Aims

The purpose of this dissertation is to examine the role of the ECG in the clinical risk assessment of patients with AF. Specifically, it addresses three key objectives:

1. To evaluate the performance of P-wave parameters in identifying patients who may not benefit from elective CV of persistent AF (Study I).
2. To identify P-wave characteristics associated with SSE in AF patients (Study II).
3. To investigate the prevalence and long-term evolution of abnormal P-wave parameters in patients with AF (Study III).

4 Materials and Methods

4.1 Study designs and patient populations

Study I

Study I is a sub-study based on the multi-center retrospective Finnish cardioversion (FinCV) 2 cohort that originally gathered patient registry data on elective electrical CVs between years the 2003 and 2015. Overall, 1,271 adult patients with persistent AF (episode duration over 48 hours) undergoing elective CV during the study period were identified from the records. A structured case report was used in data collection consisting of medical records, medications, AF history, and CV characteristics. Data were acquired over a period of 30 days, starting with the day of the procedure.

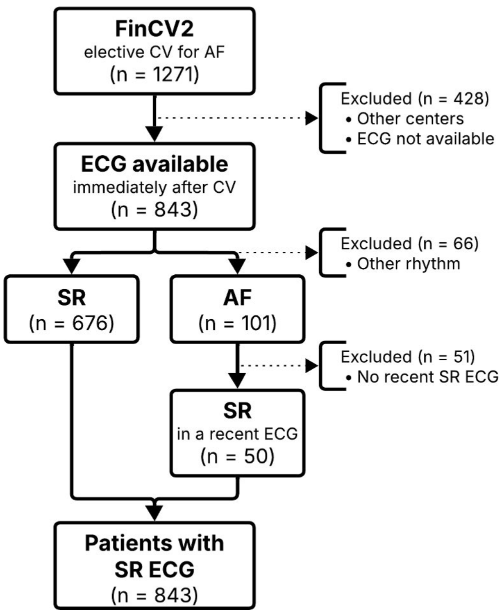

Figure 5. The number of patients screened and finally included in Study I. Patients with a failed cardioversion (CV) were searched for electrocardiograms (ECG) in sinus rhythm (SR) up to 5 years prior and 1 year after the procedure. Abbreviation: AF, atrial fibrillation. Modified from the original publication I, Figure 1.

CVs were performed under general anesthesia after confirming AF in the ECG. Paddle or pad position and the defibrillation energy used were at the discretion of the attending internist or cardiologist performing the procedure. Standard 12-lead ECGs were recorded before the CV to ensure AF as the prevalent rhythm, and after the procedure to determine the outcome.

This sub-study included only patients who received treatment within the catchment area of Turku University Hospital and had ECGs available in the electronic database (MUSE Cardiology Information System 9.0; General Electric HealthCare, Chicago, Illinois). Patients with a history of catheter ablation were also excluded due to the potential impact on P-wave quality. The database was searched for post-CV ECGs in SR from patients with a successful rhythm conversion, and SR ECGs recorded up to 60 months prior to or 12 months following CV from those with a failed rhythm conversion. Overall, 715 ECGs in SR were available. The flowchart of subject selection is presented in Figure 5.

Patients were categorized into normal P-wave, partial interatrial block (PIAB), or AIAB groups according to ECG findings. An elongated P-wave (≥ 120 ms) indicated PIAB, whereas AIAB was defined by both P-wave elongation and the presence of biphasic P-waves in all inferior leads. The main outcome of the study was ineffective CV, the composite of immediate CV failure and early AF recurrence. The procedure was deemed successful if SR was sustained through to hospital discharge. Early recurrence was defined as a new AF episode after discharge, as confirmed by an ECG or pacemaker logs.

Studies II and III

Studies II and III were a part of the FinCV 1 protocol assessing clinical challenges associated with AF. The retrospective registry study included 3,143 adult patients from three Finnish hospitals who underwent acute CV for paroxysmal AF (episode duration < 48 hours) between 2003 and 2010. Clinical data were collected using structured forms, beginning from the index CV and continuing until either AF was deemed permanent, OAC was initiated, or patient deceased. If no relevant events occurred, follow-up concluded at the date of the last recorded entry in the patient's medical record. Studies II and III only included patients from the catchment area of Turku University Hospital with electronically available ECGs.

Study II assessed the performance of various P-wave characteristics in SSE prediction. First, in the derivation phase, 1,313 patients with SR ECGs recorded immediately after the index CV were included. Potential P-wave parameters were identified by assessing their association with SSE risk within 30 days after index CV. Figure 6 illustrates how a composite variable—P-wave abnormality (PWA)—was

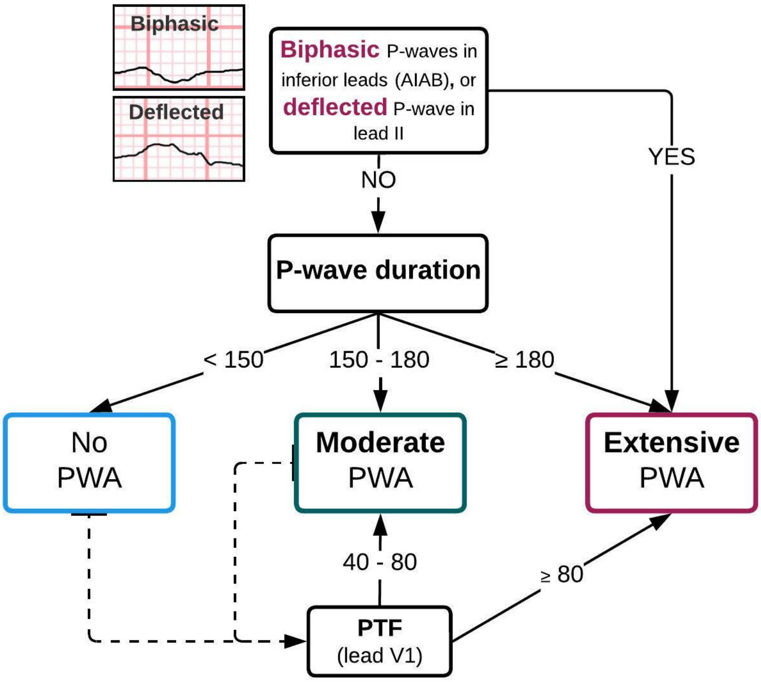

Figure 6. Patient categorization algorithm, where grouping is affected by P-wave morphology and duration as well as P-terminal force (PTF). Abbreviations: AIAB, advanced interatrial block; PWA, P-wave abnormality. From the original publication II, Figure 2.

created to classify participants into three groups based on P-wave characteristics: normal P-wave, moderate PWA, and extensive PWA.

Extensive PWA was defined by the presence of any of the following criteria: P-wave duration ≥ 180 ms, PTF ≥ 80 mm·ms, AIAB, or a deflected P-wave morphology. Moderate PWA was classified as P-wave duration between 150 and 180 ms, or PTF between 40 and 80 mm·ms, without meeting criteria for extensive PWA. Normal P-wave was defined as PTF < 40 mm·ms, P-wave duration < 150 ms, and no abnormal morphology.

Second, in the validation phase, all patients with OAC treatment and follow-up duration of less than 30 days were excluded, resulting in a final cohort of 874 subjects. The primary endpoint of the study was long-term SSE, assessed after a 30-day blanking period after the index CV and any subsequent CVs during follow-up. Secondary endpoints were all-cause death and incident heart failure.

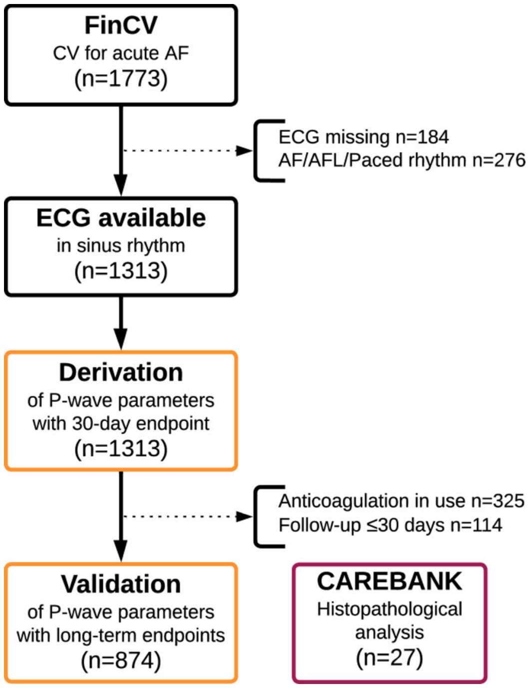

Figure 7. Study II setting demonstrating the inclusion criteria and patient numbers in derivation and validation phases. An additional sample of electrocardiograms (ECG) were collected from the CAREBANK cohort. Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; CV, cardioversion. Modified from the original publication II, Figure 1.

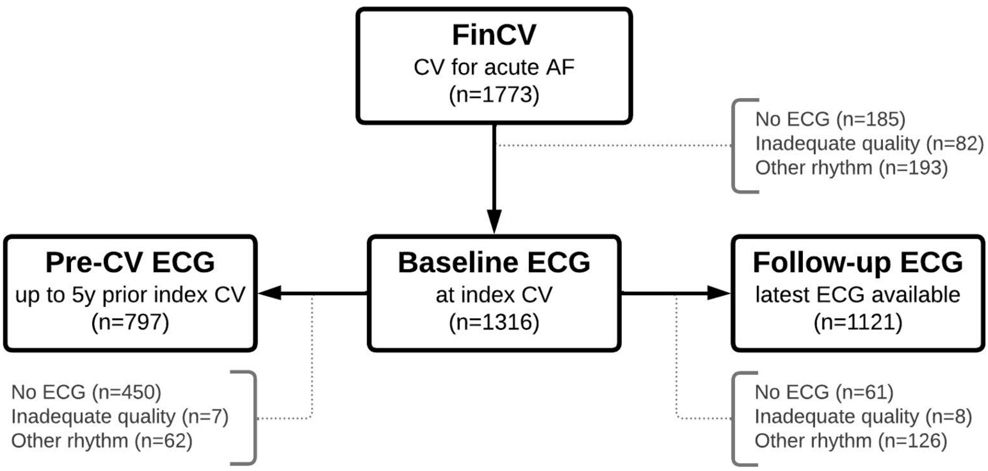

Figure 8. Flow chart of study III setting. Patients with a sinus rhythm electrocardiogram (ECG) at the index cardioversion (CV) were searched for additional ECGs prior to and after the index CV. Abbreviations: AF, atrial fibrillation. Modified from the original publication III, Supplementary Figure 1.

Third, in addition to the FinCV data, patients with paroxysmal AF undergoing cardiac surgery were identified from a separate CAREBANK[i] cohort. The CAREBANK protocol included preoperative ECGs and tissue biopsies from right atrial appendages obtained during the surgery. In total, 27 AF patients had a preoperative ECG recorded in SR combined with histopathological data. Computerized analysis was used to detect fibrosis, cardiomyocytes, and the number and size of the nuclei in hematoxylin and eosin, as well as Weigert–van Gieson stainings. This allowed for analysis of the underlying histopathology associated with the novel PWA variable. The study setting is presented in Figure 7.

Study III investigated the longitudinal stability and evolution of both the composite PWA variable and P-wave parameters individually by analyzing ECGs from multiple time points. Alongside the index ECG used in Study II, the earliest (within 5 years of the index CV) and latest available SR ECGs were retrieved from the database (Figure 8). In total, 797 patients had a pre-CV ECG, and 1,121 had a follow-up ECG, in addition to the index ECG. Due to the variability in data collection dates for the pre-CV and follow-up ECGs, only clinical data obtained at the index CV were used when analyzing risk factors for PWA progression.

4.2 Electrocardiogram interpretation

All studies utilized electronically archived standard 12-lead ECGs recorded at a speed of 50 mm/s and a voltage gain of 10 mm/mV. All measurements were made manually using digital magnification (up to 64 ×), without the use of additional tools such as calipers. The measurement precision was set at 0.25 mm (5 ms, 0.025 mV), with a line thickness of 0.15 mm. Borderline measurements were consistently rounded down.

P-wave duration was determined by simultaneously identifying the earliest onset and latest offset of baseline deviation across all limb leads. To account for signal noise and P-wave dispersion, multiple P-waves were measured, and the most representative duration was recorded.

In Studies II and III, six distinct P-wave morphologies were identified in lead II (Figure 9), in addition to the normal single-dome shape. Each P-wave pattern was assigned diagnostic criteria based on existing literature when applicable, and if a P-wave filled multiple criteria, the best fitting morphology was chosen without preference to any particular pattern. Additionally, all studies reviewed inferior leads for biphasic P-waves to diagnose AIAB. In Study I, a P-wave was considered biphasic if an initially positive deflection was followed by a negative component of

[i] CAREBANK: Cardiovascular Research Consortium—a Prospective Project to Identify Biomarkers of Morbidity and Mortality in Cardiovascular Interventional Patients

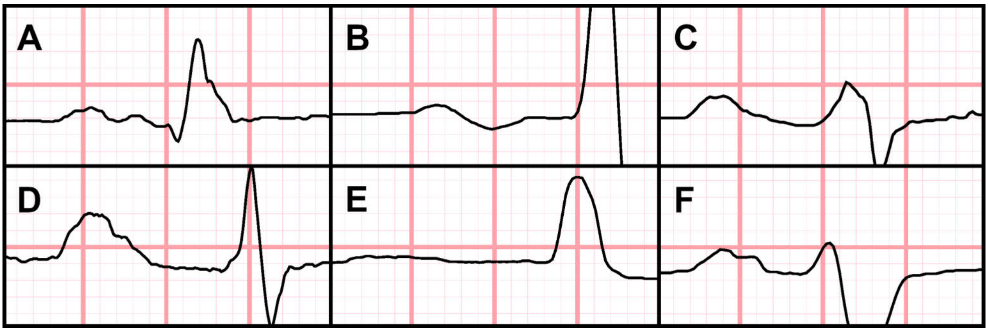

Figure 9. Variations in P-wave morphology in addition to the normal single-domed shape.
A: Bimodal – two distinct peaks at least 40 ms apart.
B: Biphasic – positive-negative wave with negative deflection ≥ 0.025 mV and ≥ 40 ms.
C: Tail – positive wave with a terminal portion comprising ≥ 50% of total P-wave duration, beginning where amplitude halves from its peak and ending at baseline.
D: Peak – tall dome-like shape with amplitude at least 0.25 mV.
E: Flat – smooth and usually long deflection with maximum amplitude < 0.05 mV
F: Deflected – single peak followed by a flattened deflection. Terminal part amplitude is over half of the maximum P-wave amplitude.

at least -0.025 mV in amplitude and 20 ms in duration. In contrast, Studies II and III required a terminal deflection -0.025 mV and 40 ms for increased sensitivity.

PTF was quantified as the product of the duration and amplitude of the negative terminal portion of the P-wave in lead V1. The terminal component was delineated from the initial downward deflection below the isoelectric line to the point at which the terminal upward slope exhibited a distinct deceleration. PTF was recorded even in the absence of a distinct initial positive deflection.

In addition to atrial P-wave analysis, the ECG was evaluated for concomitant ventricular abnormalities such as hypertrophy or conduction defects. Left ventricular hypertrophy was determined according to Sokolow-Lyon, Cornell, and modified Cornell criteria by measuring R-wave amplitudes in leads aVL, V5, and V6, along with S-wave amplitudes in leads V1 and V3 (Hancock et al., 2009). QRS complex duration and morphology were assessed to diagnose bundle branch blocks and their incomplete forms, fascicular blocks, and unspecified ventricular conduction defects according to the consensus criteria (Surawicz et al., 2009).

4.3 Statistical methods

Statistical analyses were conducted with SPSS Statistics (IBM Corporation, Armonk, New York, USA) and R (R Foundation for Statistical Computing, Vienna, Austria). In Studies I and II, SPSS version 25.0 and R version 3.5.3 were used, whereas in Study III, versions 27.0 and 4.3.1 were used, respectively. In R, the *survival, rms, timeROC, lme4,* and *lmerTest* packages were applied.

Continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data, and as median with interquartile range (25th–75th percentiles) for skewed distributions. The assumption of normality was assessed visually with Q–Q plots and histograms, and statistically evaluated with Shapiro–Wilk or Kolmogorov–Smirnov tests. Univariate analyses were performed with Kruskal–Wallis and Wilcoxon rank sum tests, as appropriate.

Categorical variables were summarized as frequencies and percentages. Pearson's chi-square and Fisher's exact tests were used to compare distributions. In Study I, the Cochran Armitage test was used to assess linear trends in proportions across multiple groups, while the linear-by-linear test was used in Study III.

A Bonferroni correction was applied for post-hoc groupwise testing. Overall, a two-sided p-value < 0.05 was considered statistically significant.

Study I

Logistic regression was used to study the association of PIAB and AIAB with CV failure, AF recurrence, and the composite outcome of ineffective CV, compared to normal P-wave. A multivariable model to predict ineffective CV was first created using the backward stepwise method, selecting variables with a p-value < 0.10. The same model was then applied to study associations with CV failure and AF recurrence.

Study II

A receiver operating characteristic (ROC) analysis was performed to determine an optimal cutoff point for PTF to predict SSE, supplementing the commonly used threshold of 40 mm·ms. Area under the curve (AUC) values were analyzed during the stepwise addition of P-wave parameters to create the composite PWA variable, aiming to optimize its predictive performance. Time-dependent ROC analysis was applied to evaluate and compare the performance of PWA, CHA_2DS_2-VASc, and their combination in predicting SSE over a 3-year follow-up period. The optimal threshold for the indicators was identified through the Youden method.

Univariable logistic regression was applied in the derivation phase to evaluate the predictive performance of different PWA models. Multivariable logistic regression was used to assess the relationship between PWA and heart failure, as the exact diagnosis date was not available for time-dependent modeling. Kaplan–Meier analysis and the Cox proportional hazards regression analysis were employed to investigate the association between PWA and mortality. The relationship between PWA and SSE was assessed using a competing risk model, with death as the competing event. All multivariable models were adjusted for the CHA_2DS_2-VASc score at the time of CV.

Study III

PWA evolution was assessed between the pre-CV and index-CV ECGs (n = 797), as well as between the index-CV and follow-up ECGs (n = 1,121). Cox proportional hazards regression was used to investigate factors associated with PWA progression. Variables with a univariable p-value < 0.10 were included in the multivariable models, except for the CHA_2DS_2-VA score, which was excluded due to its strong correlation with other covariates. The primary regression analysis compared a combined reference group—patients with either a normal P-wave or improved PWA—with those exhibiting either persistent or worsening PWA. Additional subgroup analyses were conducted to compare patients with normal P-waves to those who developed new moderate or extensive PWA. All regression analyses focused exclusively on post-CV PWA changes, as clinical data were collected at the time of the index CV.

The mean P-wave duration and its rate of change before and after the index CV were estimated using a linear mixed-effects model to account for irregular ECG collection intervals. Patient ID was modeled as a random effect. Model performance was assessed stepwise after each covariate adjustment using the Akaike Information Criterion, the Bayesian Information Criterion, Bayes factor, and analysis of variance. Only the final multivariable models are presented.

4.4 Ethical considerations

All studies were approved by the Medical Ethics Committee of the Hospital District of Southwest Finland and the ethics committee of the National Institute for Health and Welfare. The studies conform to the Declaration of Helsinki. Informed consent was obtained from participants in the CAREBANK study, whereas it was not necessary for FinCV 1 and 2 patients, owing to the retrospective design of the studies.

5 Results

5.1 Advanced interatrial block predicts ineffective cardioversion of atrial fibrillation (Study I)

PIAB was present in 524 patients (73.3%) and AIAB in 72 (10.1%). In univariate analyses, AIAB was associated with older age, hypertension, vascular disease, and reduced glomerular filtration rate. Patients with interatrial blocks also had longer PR intervals and a higher likelihood of first-degree atrioventricular block. Compared to patients with a normal P-wave (44.5 mm [40–48]), patients with PIAB had larger median LA diameter (47 mm [42–50], p = 0.041), unlike those with AIAB (44.5 mm [38–47], p = 0.800).

CV was unsuccessful in 63 cases (8.8%), including 16 patients who initially achieved successful conversion but reverted to AF before hospital discharge. Compared to patients with normal P-waves (n = 8 [6.7%]), there was no significant difference in CV failure rates in the PIAB group (n = 38 [7.3%]), whereas patients with AIAB had a significantly higher failure rate (n = 17 [23.6%], p = 0.002).

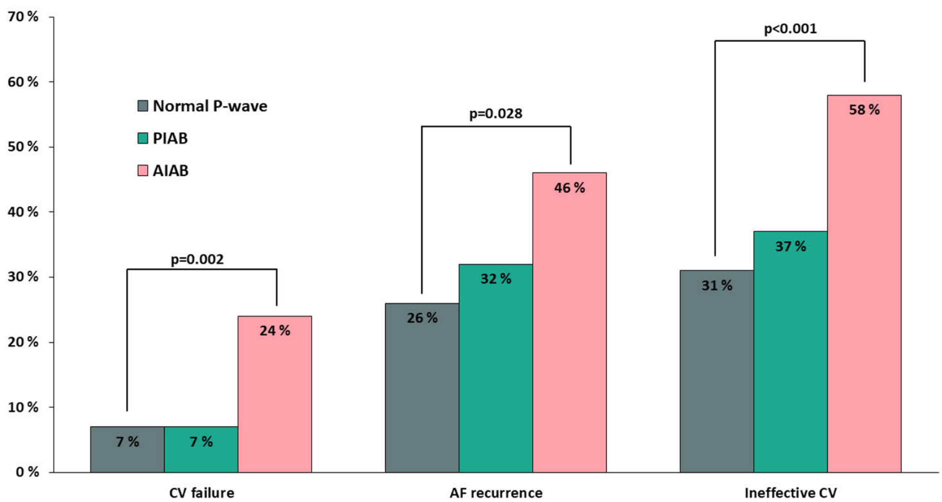

Figure 10. Incidence rates of cardioversion (CV) failure, atrial fibrillation (AF) recurrence, and the combined outcome of ineffective CV. Abbreviations: AIAB, advanced interatrial block; PIAB, partial interatrial block. From the original publication I, Figure 3.

Table 4. Multivariable regression analysis of study outcomes. Modified from the original publication I, Table 2.

	CV failure			AF recurrence			Ineffective CV		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95%CI**	**p**
AIAB	4.51	1.76–11.56	0.002	2.93	1.43–5.99	0.003	3.87	2.04–7.36	<0.001
PIAB	1.10	0.49–2.47	0.813	1.48	0.91–2.40	0.111	1.45	0.93–2.26	0.101
AV-block	0.83	0.47–1.46	0.518	0.68	0.48–0.99	0.041	0.69	0.50–0.97	0.032
Diabetes	0.73	0.33–1.63	0.444	0.54	0.32–0.91	0.021	0.55	0.35–0.89	0.014
Hypertension	1.20	0.70–2.07	0.509	1.32	0.93–1.87	0.117	1.35	0.98–1.86	0.067
AADs in use									
At CV	0.39	0.05–2.97	0.367						
At discharge				1.75	0.87–3.54	0.119	1.99	1.05–3.80	0.036

Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; AIAB, advanced interatrial block; AV-block, atrioventricular block; CI, confidence interval; CV, cardioversion; OR, odds ratio; PIAB, partial interatrial block.

Among the 652 patients with successful CV, AF recurred in 209 (29.2%) within 30 days. Individuals with AIAB were more likely to experience recurrent AF (n = 25 [45.5%]) compared to those with normal P-waves (n = 29 [26.1%], p = 0.028). In contrast the recurrence rate in the PIAB group (n = 155 [31.9%]) did not differ significantly from the normal P-wave group (p = 0.512).

Overall, CV was ineffective in 272 of the 715 (38.0%) procedures performed. A comparison between P-wave groups and study outcomes is presented in Figure 10 In multivariable logistic regression analyses, AIAB was the strongest predictor of CV failure, AF recurrence, and ineffective CV (Table 4).

5.2 Novel electrocardiographic classification for stroke prevention in atrial fibrillation patients undergoing cardioversion (Study II)

Derivation cohort

In the derivation cohort, 17 out of 1,313 (1.3%) patients suffered from SSE during the first 30 days after CV. Patients with SSE were more likely to be older, hypertensive, and have higher CHA2DS-VASc scores, with a trend toward longer P-wave duration, a higher prevalence of AIAB, and deflected P-wave morphology. In the ROC analysis, the optimal cutoff value for PTF was 80 mm·ms, yielding a sensitivity of 58.3% and a specificity of 89.5%. P-wave duration categories (< 150 ms, 150–180 ms, ≥ 180 ms) were not significant predictors of SSE in logistic regression (OR 1.8, 95% CI, 1.0–3.4, p = 0.054) or ROC analyses (AUC 0.62), whereas the inclusion of morphology and PTF categories significantly improved model performance, with an OR of 2.9 (95% CI, 1.4–5.9, p = 0.003) and an AUC of 0.70. The complete classification algorithm is presented in Figure 6.

With this model, 472 (35.9%) patients were assigned to a normal P-wave group, 521 (39.7%) to a moderate PWA group, and 320 (24.4%) to an extensive PWA group. In the respective groups, the rates for SSE were 2 (0.4%), 5 (1.0%), and 10 (3.0%, p = 0.003). In a multivariable logistic regression model, PWA was a significant predictor of 30-day SSE (OR 2.7, 95% CI, 1.3–5.5, p = 0.007).

Table 5. Baseline and follow-up characteristics stratified by P-wave abnormality categories. Modified from the original publication II, Table 2.

	P-wave abnormality					
	No (n=339)	**Moderate (n=328)**	**Extensive (n=207)**	**p†**	**p‡**	**p§**
Baseline at index cv						
Age, years	60 (50–69)	62 (54–69)	67 (58–74)	<.001	.24	<.001
≥ 65 years	123 (36.3)	134 (40.9)	119 (57.5)	<.001	.70	<.001
≥ 75 years	44 (13.0)	41 (12.5)	50 (24.2)	<.001	>.99	.003
Female sex	141 (41.6)	101 (30.8)	71 (34.3)	.01	.01	.31
Hypertension	121 (35.7)	138 (42.1)	102 (49.3)	.007	.29	.007
Heart failure	8 (2.4)	21 (6.4)	8 (3.9)	.03	.04	.93
Diabetes	22 (6.5)	40 (12.2)	20 (9.7)	.04	.04	.56
Vascular disease	45 (13.3)	51 (15.5)	50 (24.2)	.003	>.99	.005
Prior stroke or TIA	8 (2.4)	15 (4.6)	13 (6.3)	.07	.42	.11
CHA_2DS_2-VASc	1 (0–3)	1 (0–3)	2 (1–3)	<.001	.08	<.001
≥ 2	115 (33.9)	133 (40.5)	115 (55.6)	<.001	.24	<.001
Antiarrhythmic drugs¶	164 (48.7)	197 (60.8)	141 (68.1)	<.001	.006	<.001
Ventricular block	30 (8.9)	40 (12.3)	29 (14.5)	.12	.50	.19
LVH	25 (7.4)	40 (12.2)	36 (17.4)	.002	.11	.001
End of follow-up						
Duration, years	6.9 (2.6–10.9)	4.6 (1.6–10.9)	3.5 (1.2–8.1)	<.001	.03	<.001
CVs performed	2 (1–4)	2 (1–3)	1 (1–3)	.02	.21	.02
Heart failure	6 (1.8)	5 (1.5)	14 (6.8)	<.001	>.99	.01
Myocardial infarction	18 (5.3)	16 (4.9)	14 (6.8)	.64	>.99	>.99
Death	71 (20.9)	81 (24.7)	80 (38.6)	<.001	.80	<.001
SSE	11 (3.3)	13 (4.0)	27 (13.0)	<.001	>.99	<.001
At 3 years	1 (0.3)	4 (1.2)	9 (4.3)	<.001	.63	.003
At 5 years	5 (1.5)	8 (2.4)	16 (7.7)	<.001	>.99	.001
CHA_2DS_2-VASc	2 (1–3)	2 (1–3)	3 (1–4)	<.001	.92	<.001
≥ 2	197 (58.1)	208 (63.4)	154 (74.4)	<.001	.53	<.001

†Difference between all groups
‡Bonferroni corrected comparison of no PWA and moderate PWA
§ Bonferroni corrected comparison of no PWA and extensive PWA
¶Data missing on 6 cases
Data are reported as median (IQR) or count (percentage), as appropriate.
Acronym CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age ≥75 (doubled), diabetes, and prior stroke, transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74, sex category (female). Abbreviations: CV, cardioversion; LVH, left ventricular hypertrophy; SSE, stroke or systemic embolism; PTF, P-terminal force; PWA, P-wave abnormality; TIA, transient ischemic attack.

Validation cohort

After excluding patients with permanent OAC and follow-up duration ≤ 30 days, a total of 874 patients remained for further analysis. Over a median follow-up of 4.9 (1.7–9.9) years, 51 (5.8%) patients experienced SSE, 25 (2.9%) were newly diagnosed with heart failure, and 232 (26.5%) died. PWAs were frequently observed in the ECG, with 207 subjects (23.7%) showing extensive and 328 (37.5%) exhibiting moderate abnormalities. Table 5 summarizes baseline characteristics and follow-up details by PWA category, indicating that higher PWA severity was associated with greater cardiovascular burden and higher CHA_2DS_2-VASc scores.

The incidence rates of SSE were 2.7, 0.68, and 0.45 per person-years in the extensive, moderate, and no PWA groups, respectively. Figure 11 displays ROC curves comparing the ability of PWA, the CHA_2DS_2-VASc score, and their combination, to identify patients who developed SSE within 3 years.

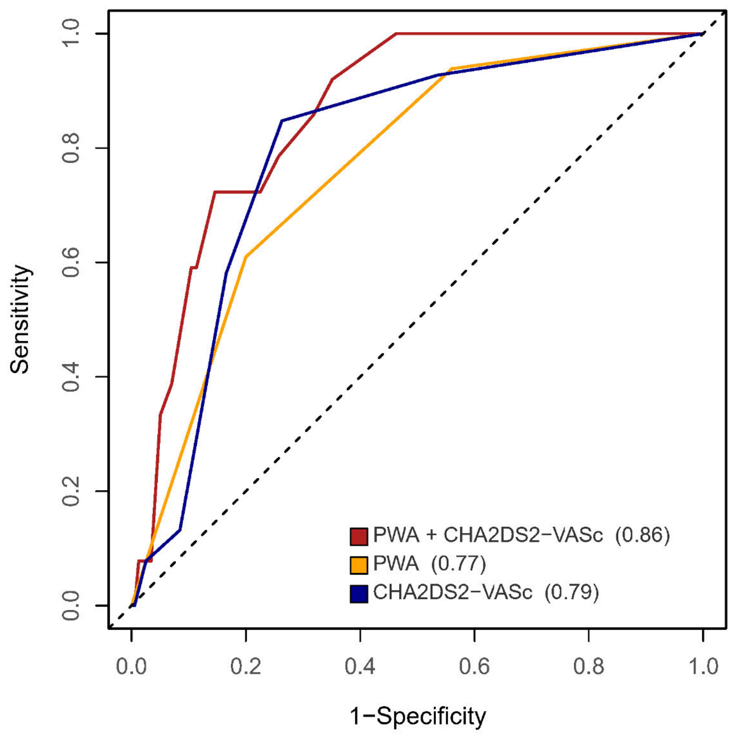

Figure 11. A time-dependent receiver operator characteristics analysis comparing the P-wave abnormality variable with CHA_2DS_2-VASc score and their combination. Area under the curve values are presented in parentheses. Acronym CHA_2DS_2-VASc indicates Congestive heart failure, Hypertension, Age ≥ 75 years (doubled), Diabetes, prior Stroke or TIA (doubled), Vascular disease, Age 65–74 years. Abbreviation: PWA, P-wave abnormality. From the original publication II, Supplementary Figure 3.

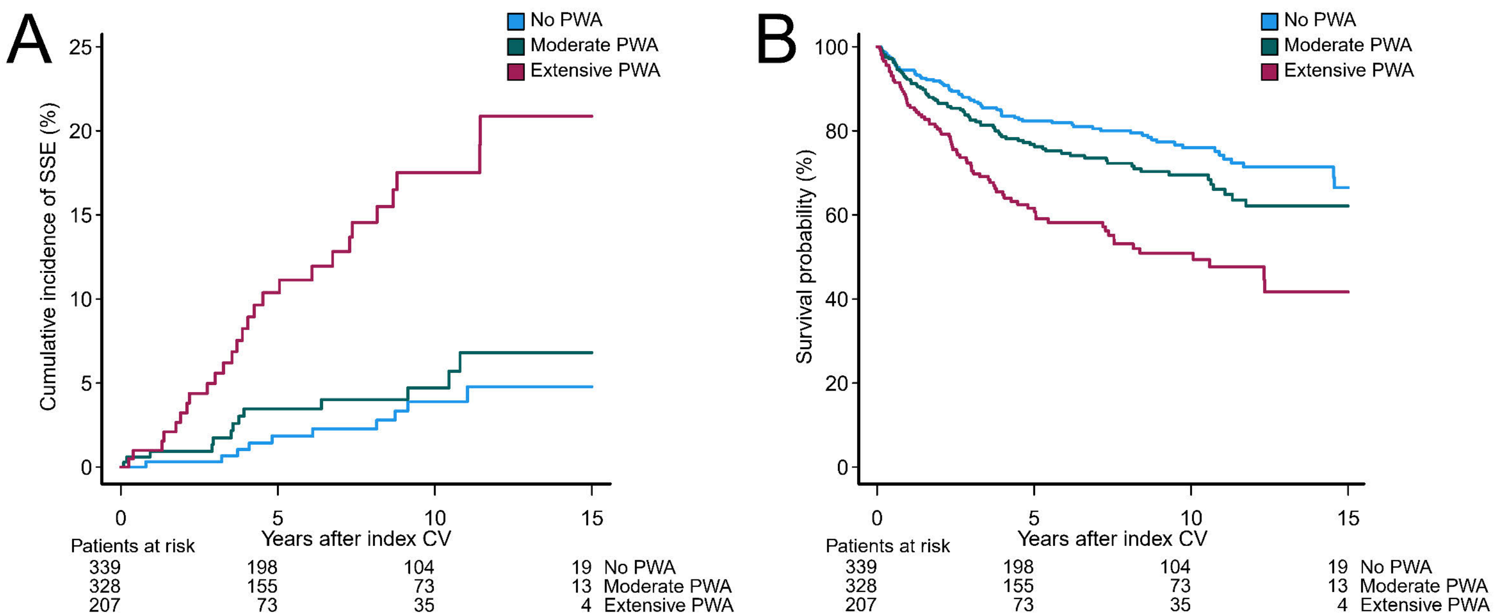

Figure 12. Study outcomes in the whole validation population categorized by P-wave abnormality (PWA) groups. Panel A depicts a cumulative incidence function of stroke or systemic embolism (SSE) in a Fine-Gray model, where death is the competing risk. Panel B is a Kaplan-Meier survival analysis. Abbreviations: CV, cardioversion. From the original publication II, Figure 3.

In a multivariable competing risk model, PWA remained independently associated with an increased risk of SSE (HR 2.1, 95% CI 1.4–3.1, $p < 0.001$), even after adjusting for the CHA_2DS_2-VASc score (HR 1.2, 95% CI 1.1–1.4, $p < 0.001$), as demonstrated in Figure 12A. Similarly, both PWA (HR 1.3, 95% CI 1.1–1.5, $p = 0.007$) and the CHA_2DS_2-VASc score (HR 1.8, 95% CI 1.6–1.9, $p < 0.001$) were significant predictors of mortality in multivariable Cox regression analysis (Figure 12B) For incident heart failure, multivariable logistic regression revealed a significant association with PWA (OR 2.1, 95% CI 1.2–3.7, $p = 0.007$), while the CHA_2DS_2-VASc score was not a significant predictor (OR 1.2, 95% CI 0.9–1.5, $p = 0.177$).

These findings were consistent in the subgroup of 511 patients with a CHA_2DS_2-VASc score < 2. In this cohort, a total of 16 (3.1%) SSE occurred, with the highest incidence in the extensive PWA group (7/92 [7.6%]), followed by moderate (6/195 [3.1%]), and no PWA (3/224 [1.3%]) groups ($p = 0.017$). PWA predicted SSE in an unadjusted competing risk analysis (HR 2.6, 95% CI 1.4–5.1, $p = 0.003$). Similarly, among patients with a CHA_2DS_2-VASc score of 0, 4/43 (9.3%) in the extensive PWA group, 2/106 (1.9%) in the moderate PWA group, and 2/145 (1.4%) in the no PWA group experienced SSE ($p = 0.021$). The association between PWA and SSE remained significant (HR 1.7, 95% CI 1.1–2.7, $p = 0.023$) in an unadjusted competing risk model.

Histopathological analysis

Tissue samples were available from 27 CAREBANK patients with known AF history, of whom 7 (25.9%) had extensive PWA, 6 (22.2%) had moderate PWA, and 14 (51.8%) had no PWA. The mean area of fibrosis was greater in those with extensive PWA (61.7×10^4 [11.1×10^4] arbitrary units), compared to those with no PWA (36.0×10^4 [4.8×10^4] arbitrary units, $p = 0.034$), whereas comparison with moderate PWA was not significant (36.0×10^4 [13.9×10^4] arbitrary units, $p = 0.088$). A visual comparison between no PWA and extensive PWA is demonstrated in Figure 13.

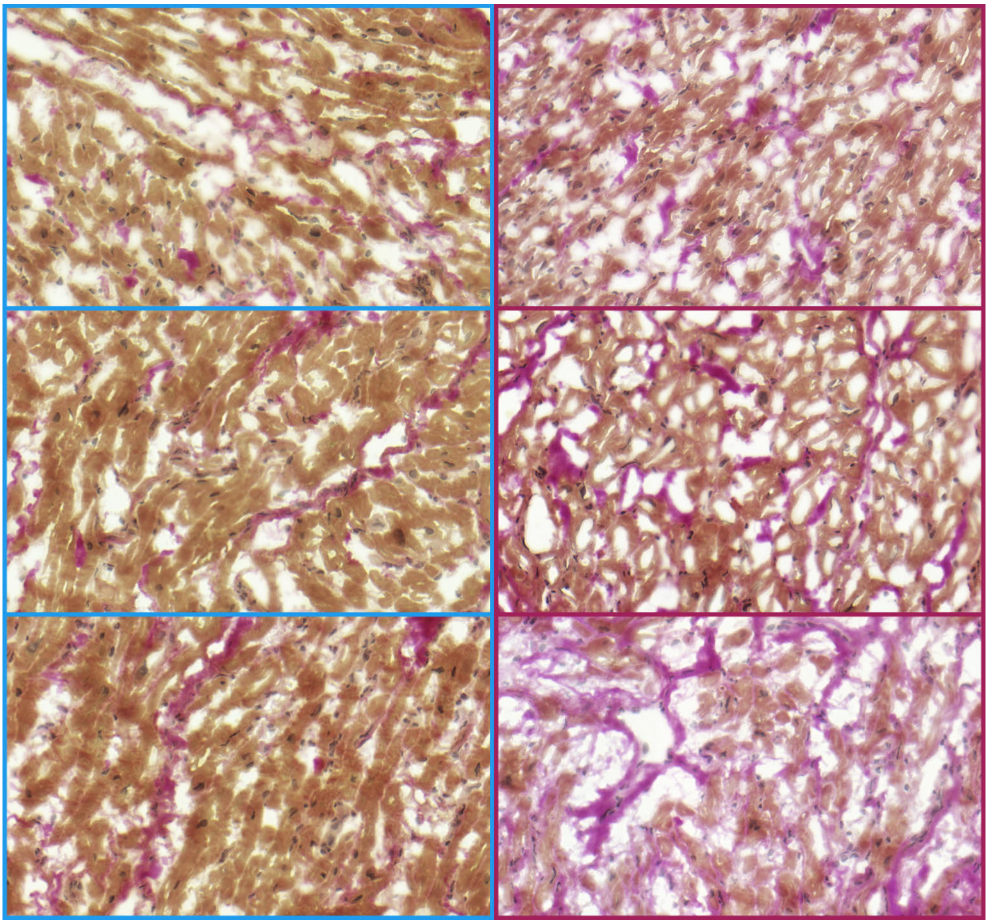

Figure 13. Histopathological comparison of right atrial appendage samples from six individual patients with history of atrial fibrillation undergoing cardiac surgery. Left-hand images represent patients with no P-wave abnormalities, while the right-hand images are from patients with extensive P-wave abnormality in the electrocardiogram. The Weigert–van Gieson stain colors normal myocardium brown and fibrous tissue purple. From the original publication II, Figure 5.

5.3 Prevalence and progression of P-wave abnormalities in patients with atrial fibrillation (Study III)

At index CV, SR ECGs were available for 1,316 patients, of whom 797 (60.5%) had a pre-CV ECG and 1,121 (85.2%) had a follow-up ECG. The median time between the pre-CV and index recordings was 2.6 (1.0–4.1) years, and between index and post-CV recordings, 6.1 (2.5–10.3) years. Patient flow between PWA categories across successive ECGs is shown in Figure 14.

Changes in the P-wave abnormality categories after the index cardioversion

Baseline characteristics grouped by PWA categories at the time of the index CV are presented in Table 6. After the index CV, AF recurred within 30 days in 47 (11.5%), 62 (13.7%) and 52 (20.0%) cases with a normal P-wave, moderate PWA, and extensive PWA, respectively ($p = 0.009$). Similarly, a high CV frequency (time between procedures < 180 days) was observed in 42 (11.4%), 59 (14.8%), and 52 (21.6%) patients in the respective groups ($p = 0.003$).

PWA progression was more frequently observed in ECGs from patients in the longest follow-up quartile compared to those in the shortest quartile ($p = 0.002$ for trend; see Figure 15). Risk factors for PWA evolution were evaluated using a composite outcome that grouped progressed or persistent PWA versus improved PWA or persistently normal P-waves. The results of the Cox regression analyses are presented in Table 7. In subgroup analyses, age (HR 1.04, 95% CI 1.01–1.06, $p = 0.001$), heart failure (HR 1.15, 95% CI 1.03–9.77, $p = 0.045$), AF recurrence within 30 days of index CV (HR 1.92, 95% CI 1.06–3.49, $p = 0.033$) and left ventricular hypertrophy (HR 2.86, 95% CI 1.69–4.84, $p < 0.001$) predicted progression from normal P-wave to moderate PWA, while age (HR 1.06, 95% CI 1.03–1.09, $p < 0.001$) was the only significant predictor for developing new extensive PWA from normal P-wave.

Changes in individual P-wave parameters

The individual P-wave parameters contributing to the composite PWA at each time point are provided in Table 8. Using a linear mixed-effects model without covariates, the estimated P-wave duration was 136.45 ms (standard error 1.23 ms) five years before the index CV, with an annual increase of 1.12 ms (standard error 0.28). In a multivariable model, age beyond 65 years, male sex, and history of AF episodes increased the average P-wave duration, while patients with their first AF episode had a steeper increase in duration over time.

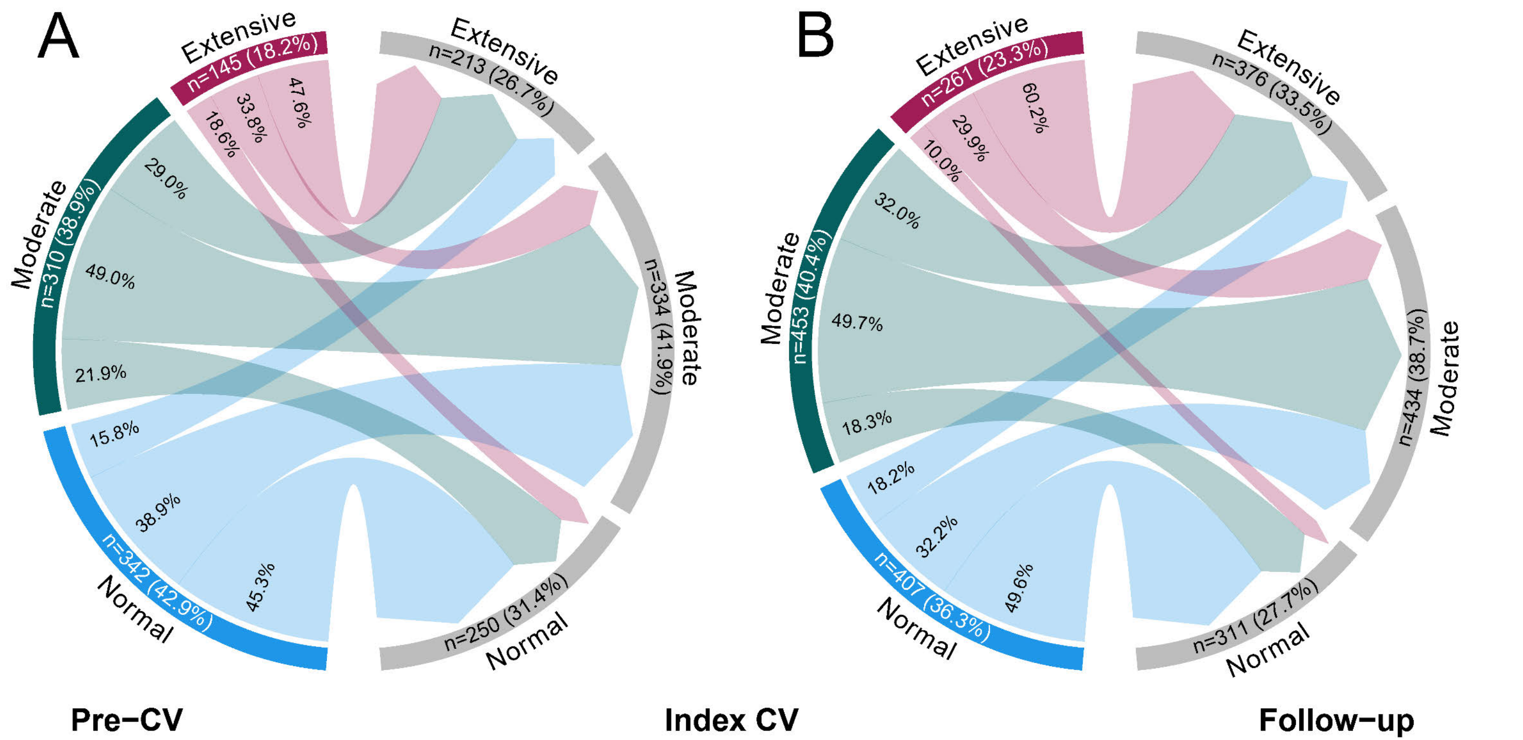

Figure 14. Evolution of P-wave abnormality (PWA) categories. Panel A illustrates changes between pre-cardioversion (CV) and index CV electrocardiograms (ECGs) (n = 797), whereas panel B depicts change between index CV and follow-up ECGs (n = 1,121). From the original publication III, Figure 1.

Table 6. Clinical characteristics of patients with P-wave abnormality at index cardioversion. Modified from the original publication III, Table 1.

	P-wave abnormality					
	Normal (n = 407)	**Moderate (n = 453)**	**Extensive (n = 261)**	**p†**	**p‡**	**p§**
Age, years	61 (53–71)	63 (55–71)	66 (58–73)	<0.001	0.180	<0.001
≥ 65 years	161 (39.6)	206 (45.5)	147 (56.3)	<0.001	0.255	<0.001
≥ 75 years	59 (14.5)	67 (14.8)	56 (21.5)	0.033	0.999	0.064
Male sex	227 (55.8)	300 (66.2)	165 (63.2)	0.006	0.006	0.192
Heart failure	11 (2.7)	24 (5.3)	14 (5.4)	0.119	0.012	0.031
Hypertension	156 (38.3)	218 (48.1)	127 (48.7)	0.005	0.177	0.282
Diabetes	37 (9.1)	62 (13.7)	33 (12.6)	0.1	0.126	0.465
Prior stroke or TIA	19 (4.7)	31 (6.8)	18 (6.9)	0.334	0.573	0.687
Vascular disease	66 (16.2)	97 (21.4)	77 (29.5)	<0.001	0.168	<0.001
CHA_2DS_2–VA	1 (0–2)	1 (0–3)	2 (1–3)	<0.001	0.001	<0.001
≥ 2	142 (34.9)	205 (45.3)	144 (55.2)	<0.001	0.007	<0.001
Previous AF episodes	248 (60.9)	291 (64.2)	175 (67.0)	0.263	0.972	0.354
Any AAD	217 (53.8)	295 (66.1)	191 (74.3)	<0.001	<0.001	<0.001
Class I or III AAD	58 (12.6)	63 (12.0)	65 (20.1)	0.002	0.999	0.015
Wide QRS	19 (4.7)	33 (7.3)	28 (10.7)	0.012	0.351	0.014
LVH	48 (12.0)	89 (20.0)	56 (22.3)	<0.001	0.006	0.002

† Difference between all groups
‡ Bonferroni corrected comparison of normal P-wave and moderate PWA
§ Bonferroni corrected comparison of normal P-wave and extensive PWA
The total number of patients amounts to 1121 to ensure uniform presentation of the data with further analyses. Data are reported as median (IQR) or count (percentage), as appropriate. Acronym CHA2DS2-VA indicates congestive heart failure, hypertension, age ≥75 (doubled), diabetes, and prior stroke, transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74. Abbreviations: AAD, antiarrhythmic drugs; AF, atrial fibrillation; CV, cardioversion; LVH, left ventricular hypertrophy; TIA, transient ischemic attack.

Table 7. Risk factors for persistent or progressed P-wave abnormality (PWA) after index cardioversion. Modified from the original publication III, Table 2.

	Univariable			Multivariable		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**p**
Age, per year	1.04	(1.03–1.05)	<0.001	1.03	(1.03–1.04)	<0.001
Male sex	0.88	(0.76–1.02)	0.095	1.15	(0.98–1.37)	0.096
Heart failure	1.84	(1.30–2.61)	<0.001	1.56	(1.05–2.33)	0.027
Hypertension	1.75	(1.51–2.02)	<0.001	1.37	(1.15–1.63)	<0.001
Diabetes	1.42	(1.14–1.77)	0.002	1.05	(0.81–1.36)	0.701
Previous stroke or TIA	1.77	(1.33–2.36)	<0.001	1.03	(0.73–1.46)	0.852
Vascular disease	1.88	(1.58–2.24)	<0.001	1.28	(1.04–1.46)	0.020
CHA_2DS_2–VA	1.38	(1.32–1.45)	<0.001	1.20	(1.01–1.43)	
Previous AF episodes	1.32	(1.13–1.54)	<0.001	1.20	(0.95–1.53)	0.043
Early AF recurrence†	1.35	(1.11–1.65)	0.003	1.30	(1.03–1.64)	0.130
High CV frequency‡	1.88	(1.52–2.32)	<0.001	0.99	(0.83–1.20)	0.026
Any AAD	1.54	(1.32–1.81)	<0.001	1.74	(1.27–2.38)	0.943
Class I or III AAD	0.95	(0.77–1.18)	0.639	1.33	(1.08–1.65)	
Wide QRS	1.78	(1.37–2.31)	<0.001	1.03	(1.03–1.04)	<0.001
LVH	1.59	(1.32–1.92)	<0.001	1.15	(0.98–1.37)	0.007

† Recurrence within 30 days after the index CV

‡ High CV frequency: an interval between procedures <180 days

Hazard ratios (HRs) are calculated with a Cox regression analysis comparing the composite of progressed or persistent PWA status (n = 732) with improved PWA or consistently normal P-wave (n = 389). Acronym CHA2DS2-VA indicates congestive heart failure, hypertension, age ≥75 (doubled), diabetes, and prior stroke, transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74. Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; CI, confidence interval; CV, cardioversion; LVH, left ventricular hypertrophy; TIA, transient ischemic attack.

At the time of index CV, the unadjusted model estimated the P-wave duration at 143.45 ms (standard error 0.76), increasing at a rate of 1.24 ms per year (standard error 0.08). Similarly, in the multivariable model age beyond 65 years, male sex, hypertension, vascular disease, high CV frequency, wide QRS complex, and left ventricular hypertrophy were associated with longer P-waves. Figure 16 illustrates simple projections of pre-CV and post-CV models.

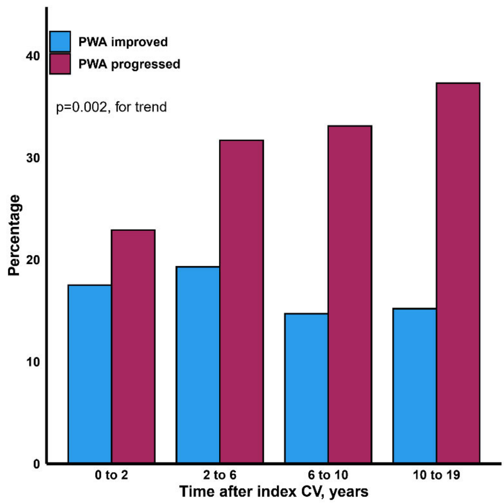

Figure 15. Temporal distribution of P-wave abnormality (PWA) improvement or progression over follow-up. Abbreviations: CV, cardioversion. From the original publication III, Figure 2.

Table 8. Distribution of individual P-wave abnormalities across study electrocardiograms. Modified from the original publication III, Supplementary Table 2.

	Pre-CV (n = 797)	Index (n = 1316)	Follow-up (n = 1121)	p†	p‡
P-wave duration, ms					
≥ 150	257 (32.2)	485 (36.9)	598 (53.3)	<0.001	<0.001
≥ 180	39 (4.9)	124 (9.4)	194 (17.3)	<0.001	<0.001
PTF, mm·ms§					
≥ 40	287 (37.6)	546 (42.5)	413 (36.8)	<0.001	0.017
≥ 80	64 (8.0)	110 (8.6)	75 (7.0)	0.121	0.095
AIAB	27 (3.4)	91 (6.9)	139 (12.4)	0.002	<0.001
Deflected morphology	31 (3.9)	57 (4.3)	63 (5.6)	0.419	0.256

† McNemar comparison between pre-CV and index CV groups (n=797)
‡ McNemar comparison between index CV and follow-up groups (n=1121)
§ PTF could not be analyzed in 34, 32 and 54 cases, respectively
Abbreviations: AIAB, advanced interatrial block; PTF, P-terminal force.

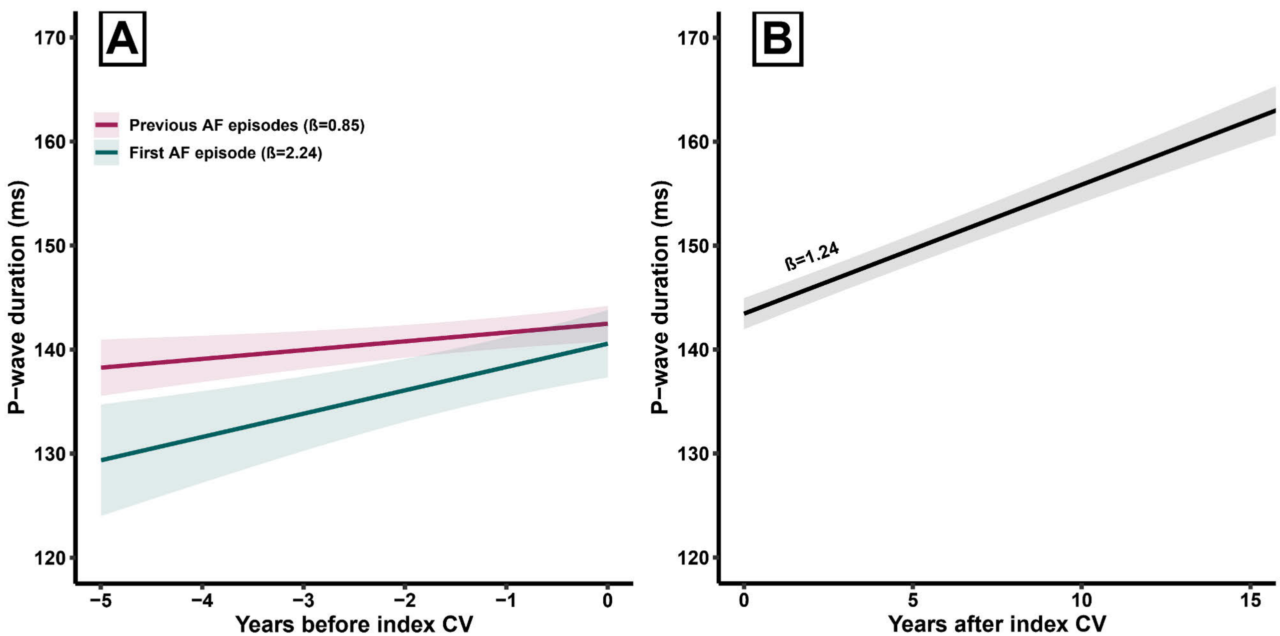

Figure 16. Estimations of average P-wave progression in linear mixed effects models before (Panel A) and after (Panel B) the index cardioversion (CV). Panel A is adjusted for previous AF history to highlight the difference in slopes (β). The shaded area represents 95% confidence intervals. Abbreviation: AF, atrial fibrillation. From the original publication III, Figure 4.

6 Discussion

6.1 Advanced interatrial block predicts ineffective cardioversion of atrial fibrillation

Study I identified AIAB as a strong predictor of both CV failure and AF recurrence when each outcome was assessed independently. Notably, approximately two-thirds of CVs were ineffective in patients with AIAB, with the odds being nearly fourfold higher compared to those without this ECG finding. While the association of AIAB and AF recurrence is aligned with previous small-scale studies (Fujimoto et al., 2018; Gonna et al., 2014), data on ECG parameters predicting immediate CV failure have not been previously reported.

In univariate analyses, PIAB was associated with larger LA diameter, whereas AIAB was correlated with other established risk factors for aCM, including older age, hypertension, and vascular disease—highlighting the multifactorial nature of atrial remodeling. It is well established that older patients with LA enlargement are less likely to maintain SR (Jaakkola et al., 2017; Van Gelder et al., 2024), yet unlike AIAB, neither PIAB nor other aCM-associated variables predicted the study outcomes. Nevertheless, these findings suggest that only more pronounced markers of underlying aCM, such as AIAB, seem to influence AF burden.

Study I also indicated that interatrial blocks are more prevalent among patients with AF than in the general population. AIAB was present in 10% of patients undergoing CV for persistent AF, and PIAB in approximately 75%, compared to reported rates of about 1% and 10%, respectively, in the general population (Istolahti et al., 2020). This distinction is clinically relevant, as AIAB has been strongly linked to new-onset AF (Istolahti et al., 2020; Martínez-Sellés et al., 2020). Our findings further support this association, demonstrating a nearly fourfold increase in the odds of ineffective CV in patients with AIAB. Importantly, the clinical relevance of AIAB is amplified by its independent association with SSE, underscoring the potential clinical utility of P-wave analysis in the ECG.

Overall, efforts to identify patients unlikely to benefit from CV of persistent AF have achieved only modest success to date (Hellman et al., 2017; Kuppahally et al., 2009; Raitt et al., 2006). Notably, many established predictors are assessed only after the CV procedure, limiting their utility in pre-procedural decision-making. In contrast, AIAB can often be detected from ECGs recorded prior to the onset of AF. Our findings suggest that, alongside standard clinical evaluation, reviewing historical ECGs could aid in identifying patients less likely to benefit from an elective CV. This is particularly relevant given that ECGs are frequently recorded and stored electronically as part of routine care. Moreover, post-CV ECGs should also be interpreted carefully, with any findings of AIAB documented to inform future treatment decisions.

In summary, interatrial blocks are a common phenomenon in patients with persistent AF. Among these, AIAB stands out as a strong, independent predictor of ineffective CV. Given its prevalence and prognostic value, routine assessment of ECGs—including prior recordings—may help guide patient selection for elective CV and improve clinical decision-making.

6.2 Novel electrocardiographic classification for stroke prediction in atrial fibrillation patients undergoing cardioversion

Study II demonstrated that ECG offers additional insight into the susceptibility to SSE, heart failure, and mortality in non-anticoagulated AF patients. Patients with extensive PWA had nearly a fourfold increased risk of SSE and a twofold increased risk of death compared to those without PWA, even after adjusting for the CHA_2DS_2-VASc score. Likewise, the risk of heart failure was approximately tripled. Previous studies have established similar results with individual P-wave parameters,(L. Y. Chen et al., 2022) but none have examined atrial ECG changes as comprehensively in an effort to improve risk stratification in patients with AF.

In line with our results, P-wave elongation was associated with SSE after adjusting for the CHA_2DS_2-VASc score in a recent multi-center study utilizing data from over 500,000 ECGs (Lampert et al., 2023). However, that study focused solely on P-wave duration and did not account for other relevant markers such as PTF or biphasic morphology, which may offer additional prognostic value (Istolahti et al., 2020; Kamel et al., 2015; O'Neal, Zhang, et al., 2016). Similarly, Maheshwari et al reported that adding points to the CHA_2DS_2-VASc score for having an abnormal P-wave axis improved the C-statistic of 1-year stroke prediction to a modest 0.75 (Maheshwari et al., 2019). However, their model omitted AIAB and PTF, both of which were found associated with stroke risk. Nevertheless, in Study II, the model combining PWA and CHA_2DS_2-VASc score yielded a significantly greater C-statistic of 0.86 for 3-year stroke prediction.

In contrast to the risk of SSE, incident heart failure is a less commonly reported outcome in ECG-related research. Nonetheless, associations have been observed with both prolonged P-wave duration and increased PTF (Eranti et al., 2014;

Lampert et al., 2023). Likewise, the prevalence of elongated P-waves and AIAB appears higher among patients with heart failure (21% and 24%, respectively) compared to the general population (10% and 1%) (Escobar-Robledo et al., 2018; Istolahti et al., 2020). Additionally, an elevated risk of all-cause and cardiac mortality has been linked to prolonged P-waves, AIAB, and PTF. Notably, Eranti et al. reported that a PTF threshold of ≥ 60 mm·ms was a stronger predictor of mortality than the conventional ≥ 40 mm·ms cut-off (Eranti et al., 2014).

The basis of the novel PWA categorization was P-wave duration classification introduced by Müller-Edenborn et al. (Müller-Edenborn, Chen, et al., 2020; Müller-Edenborn et al., 2022). Their studies demonstrated that P-waves beyond 180 ms in duration were associated with low-voltage areas in EAM, the presence of thrombi in echocardiography, and increased incidence of adverse cardiac and cerebrovascular events in clinical practice. The incorporation of AIAB and PTF into the PWA classification enhances its value by capturing distinct aspects of atrial pathology: AIAB is associated with conduction block at the Bachmann bundle, while PTF reflects LA enlargement (Bayés De Luna et al., 2012; L. Y. Chen & Soliman, 2019). Notably, low-voltage areas, interatrial blocks, and LA enlargement are all considered manifestations of underlying aCM (Goette et al., 2024). Furthermore, in Study II, extensive PWA was linked to atrial fibrosis, another hallmark feature of aCM, reinforcing the relevance of these ECG findings in identifying structural and electrophysiological atrial disease.

The results from Study II suggest that ECG may offer additional value when evaluating the need for OAC to prevent AF-related SSE in borderline-risk patients. Current guidelines recommend considering anticoagulation when a patient has only one CHA_2DS_2-VASc point, and withholding treatment when the score is zero (Joglar et al., 2024; Van Gelder et al., 2024). In this cohort, patients with extensive PWA demonstrated an elevated risk of SSE regardless of their clinical score. These findings support the consideration of ECG markers of extensive PWA when deciding on long-term anticoagulation after CV in patients with borderline CHA_2DS_2-VASc scores.

In conclusion, PWA offered additional prognostic insight into SSE risk among AF patients. Incorporating this ECG information may aid in anticoagulation decisions for those at borderline risk.

6.3 Prevalence and progression of P-wave abnormalities in patients with atrial fibrillation

The repeated ECGs from 1,316 patients in Study III show that PWAs are a slowly progressing phenomenon. Two-thirds of patients with PWA on the pre-CV ECG showed either stable or progressed patterns at the time of index CV, while only one in five had reverted to a normal P-wave. At follow-up, the corresponding proportions were 74% and 15%. Progression in PWA categories was more pronounced over longer follow-up periods, primarily driven by a gradual increase in P-wave duration. As expected, advancing age and chronic cardiovascular conditions were predictors of PWA progression.

PWA, as a composite variable, was originally introduced in Study II and therefore, the study lacks data on its prevalence or incidence. The prevalence of individual P-wave parameters, however, is better documented and varies considerably. In the general population, AIAB is observed in approximately 1%, while PTF $\geq$ 40 mm·ms is reported in 2–16% (Eranti et al., 2014; Istolahti et al., 2022; Lehtonen et al., 2017). Among patients with AF, Study I reported AIAB in over 10% of cases, while PTF was observed in more than 20% (Sudo et al. 2023). In the present study, the prevalence of AIAB ranged from 3% to 12%, and PTF from 36% to 42%. It should be noted, however, that studies may use varying methods for AIAB diagnosis, as was the case between in Studies I and II/III. Overall, the prevalence of PWA increased at each time point, with 70% of patients exhibiting some degree of PWA by the end of follow-up, although some cases showed normalization.

Research on the progression of individual P-wave abnormalities is limited but generally consistent with our findings. Longitudinal studies have linked new occurrences of elongated P-wave ($\geq$ 120 ms), AIAB, and PTF to aging and cardiovascular risk factors such as hypertension and vascular disease (Istolahti et al., 2022; Lehtonen et al., 2017). Consistent with these observations, age, heart failure, and other comorbidities were the strongest predictors of progressive or persistent PWA in our study, with higher CHA_2DS_2–VA scores also forecasting similar outcomes. Subgroup analyses further confirmed these trends in the progression from normal P-wave to moderate or extensive PWA. Cross-sectional studies similarly show longer P-waves in older individuals, though no significant elongation was observed over a 3-year follow-up period (Havmöller et al., 2009; Magnani et al., 2010; J. B. Nielsen et al., 2015). In Study III, linear mixed-effects models revealed a modest annual increase in P-wave duration, which likely accumulates into clinically meaningful progression over longer periods.

In addition to age and comorbidities, prior AF history and frequent CVs predicted PWA progression. Patients with extensive PWA were also more prone to early AF recurrence (within 30 days) after the index CV. Although precise AF burden data were not available, these factors may serve as indirect indicators of increased episode frequency, which can drive atrial remodeling (M. Li et al., 2022). Conversely, effective rhythm control and maintenance of SR appear to reverse underlying electromechanical changes (Goette et al., 2024). Despite over two-thirds of patients using AADs, these medications did not significantly impact PWA progression in multivariable analyses, even though Class I and III agents are known to influence P-wave morphology and duration (Lei et al., 2018).

While transitions between PWA categories may reflect true physiological changes, the exact underlying pathophysiology remains unclear. Fibrosis is likely the end stage of this continuum (Alexander et al., 2021; Goette et al., 2024; Yamaguchi et al., 2022), as indicated by the association between extensive PWA and a larger burden of fibrotic myocardial tissue compared to normal P-waves in Study II. However, prior to fibrosis, the atria may undergo a range of structural and electrical alterations (Liu et al., 2025; D. Qiu et al., 2021). AIAB specifically reflects conduction impairment at the Bachmann bundle and, together with prolonged P-wave duration and PTF, has been linked to reduced atrial contractility and low-voltage areas in EAM studies (Alexander et al., 2021; Bayés De Luna et al., 2012; McConkey et al., 2021; Müller-Edenborn et al., 2022). Both AIAB and PTF are strongly associated with LA enlargement, which may precede conduction defects (Alexander et al., 2021; Bayés De Luna et al., 2012). Notably, one recent study found that PTF correlated more with electrical remodeling than with atrial enlargement (Lebek et al., 2021). Histology from that study showed less fibrosis in cases with higher PTF values, possibly because viable cardiomyocytes produce larger terminal amplitudes. These observations suggest that different PWA components may reflect distinct stages or aspects of atrial remodeling beyond fibrosis alone.

In addition to biomarkers, imaging, and electrophysiological evaluation of atrial size and function, various P-wave components have been proposed as supportive markers in diagnosing aCM, which is currently assessed only through histology (Table 3) (Goette et al., 2024; M. Li et al., 2022). While the composite PWA variable has not been formally validated as a marker of aCM, it shares several key characteristics. aCM is defined as an electromechanical atrial disorder capable of producing clinically significant outcomes, primarily driven by aging and exacerbated by comorbidities (Goette et al., 2024). Its strong association with AF is well established, although the exact nature of this relationship is not completely understood (Goette et al., 2024; M. Li et al., 2022). In Study II, PWA was linked to atrial fibrosis, SSE, heart failure, and mortality in AF patients. Its progression appears to follow a similar trajectory to aCM, with aging and chronic cardiovascular disease acting as major contributors, and factors such as prior AF or high CV frequency further increasing the likelihood of worsening PWA. Nonetheless, the underlying pathophysiological mechanisms of PWA remain to be fully elucidated and warrant further investigation to establish their role as a marker of aCM.

Taken together, these findings highlight the progressive and persistent nature of PWAs in patients with paroxysmal AF, primarily driven by aging, chronic cardiovascular diseases, and frequent AF recurrences. This supports the potential clinical value of PWA classification as an indicator of AF-related complications.

While limited by statistical power, the results align with current recommendations emphasizing early rhythm control and management of comorbidities, which may also mitigate PWA progression.

6.4 Strengths and limitations

All Studies included herein (I–III) have the inherent limitations of single-center retrospective designs. However, data collection was standardized using a structured case report form to ensure consistency across cases. In addition to detailed patient characteristics, ECGs, and study outcomes retrieved from local records, Study II also included cause-of-death data retrieved from the national registry, Statistics Finland.

All ECG characteristics were assessed manually using digital magnification without automated tools to increase the clinical applicability of the findings. ECG analyses were performed by a single observer in Studies I and II, and two observers in Study III, all blinded to study outcomes. Although only Study II reported intraobserver reliability, which ranged from good to excellent, the same observer performed ECG analyses in all three studies and conducted the majority of analyses in Study III. In Study I, intraobserver reliability was not formally assessed; however, repeat ECG measurements were performed to rule out atrial stunning, and no marked changes were observed between the two recordings. In Study III, a second observer was trained by the first observer, and good interobserver agreement was ensured before analyzing study ECG, although the corresponding data are not shown.

In Study I, AF detection following hospital discharge relied on ECGs recorded at 30-day follow-up visits and during symptomatic or otherwise clinically indicated episodes, rather than continuous monitoring. As a result, asymptomatic or self-terminating AF episodes were likely underdetected, and the true recurrence rate may have been higher.

Study II excluded patients with unsuccessful CV by design, as only post-CV ECGs in SR were analyzed. Other than this, no exclusion criteria were applied that would have affected the assessment of SSE outcomes.

In Study III, pre-CV and follow-up ECGs were not recorded at fixed intervals, introducing variability in the timing of PWA progression assessments. Nonetheless, the large sample size ensured adequate temporal distribution of ECGs, and the linear mixed-effects model accounted for individual data collection dates when assessing changes in P-wave duration. Furthermore, the absence of imaging and biomarker data limited the ability to correlate PWA progression directly with atrial remodeling, which may have provided deeper insight into the underlying pathophysiology and aCM.

6.5 Future perspectives

Studies I and II demonstrated that abnormal P-wave parameters are associated with increased risk of ineffective CV, SSE, heart failure, and death. Study III further showed that even previously recorded ECGs can provide valuable prognostic information. In future practice, reviewing past ECGs may offer an accessible and cost-effective approach to identifying patients who may require closer monitoring, potentially before overt clinical deterioration occurs.

Nevertheless, several important questions remain. Although the risk of SSE is pronounced in patients with extensive PWA—independent of their clinical CHA_2DS_2-VASc scores—it is still uncertain whether the potential benefits of OAC outweigh the associated bleeding risk in this group. Future prospective trials are essential to evaluate whether PWA categorization can be effectively integrated into anticoagulation decision-making, especially for patients otherwise classified as low risk by traditional clinical scoring systems. Additionally, improved phenotyping of PWAs using EAM, imaging, biomarkers, and histological analysis may help delineate the diverse pathways of atrial remodeling and refine the classification of aCM. As this study focused solely on ECGs of patients with established AF, the potential role of PWAs as early markers of aCM or future AF in individuals without known arrhythmia remains unexplored.

Ultimately, a deeper understanding of PWAs could pave the way for earlier AF diagnosis and support targeted interventions aimed at preventing disease progression and reducing AF-related complications, thereby improving long-term outcomes.

7 Conclusions

This research provides comprehensive insight into the utility of P-wave parameters in assessing individual risk for AF-related complications. By exploring the progression, clinical significance, and histopathology related to PWAs, the work advances current knowledge of AF and aCM. Specifically, the main conclusions of this thesis are:

1. ECG may be used to identify patients who will not benefit from an elective CV.
2. Novel electrocardiographic PWA classification provides additional prognostic insight in AF patients over conventional risk assessment with the CHA_2DS_2-VASc score.
3. The prevalence and rate of progression of PWAs are high in AF patients, with change driven by classic cardiovascular risk factors.

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Turku, December 2025
Arto Relander

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