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Risk factors for incident heart failure and atrial fibrillation in an elderly population

The role of cardiac conduction and heart rate variability

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Abstract
Ostrowska, B. 2024. Risk factors for incident heart failure and atrial fibrillation in an elderly population. The role of cardiac conduction and heart rate variability. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 2007. 57 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-2002-1.

Heart failure (HF) and atrial fibrillation (AF) are epidemic diseases, frequently coexisting, sharing risk factors and conferring poor prognosis. Identification of individuals at high risk of HF and AF may enable early treatment and improve the prognosis. Reliable prediction models for daily clinical practice are lacking. Early modification and treatment of risk factors may reduce the incidence of AF and HF. Because atrial structure and function abnormalities increase the risk of AF, ECG indices reflecting atrial pathology may prove useful in predicting AF and HF.

The main objectives were to evaluate whether:

• P-wave duration (Pdur) and PR-interval in V1 predicted incident HF and incident AF (Paper I-II)
• low frequency/high frequency (L-F/H-F) ratio, a marker of autonomic balance, predicted incident HF (Paper IV)
• combining selected ECG variables or the L-F/H-F ratio with traditional risk factors improved the performance of the traditional HF prediction model (Paper III-IV).

The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) with 15 years of follow-up was used for all four studies. After applying the exclusion criteria, 836 subjects were evaluated for incident HF (Paper I, III-IV) and 877 subjects for incident AF (Paper II). Cox proportional hazard analysis related ECG-derived variables to incident HF and incident AF. Study III used machine learning to determine which ECG variables correlated to incident HF. C-statistic was used to test whether adding selected ECG variables to traditional HF risk factors improved the performance of the HF prediction model.

Short Pdur was significantly associated with incident HF (Paper I) and incident AF (Paper II). Of 134 ECG variables, high R-wave amplitude variation (SD Ramp) had the highest predictive value for HF (Paper III). A decreased L-F/H-F ratio significantly predicted HF (Paper IV). Adding eight selected ECG variables (Paper III) and the L-F/H-F ratio (Paper IV) to the traditional risk factors significantly improved HF predictive performance by 11.7% and 3.3%, respectively.

In conclusion, the ECG may prove useful for predicting incident HF and AF beyond the traditional risk factors. An autonomic imbalance may precede the development of HF.

Keywords: incident heart failure, incident atrial fibrillation, prediction of heart failure, short P-wave duration, heart rate variability.

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To my beloved family

List of Papers

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

I. Ostrowska B, Lind L, Sciaraffia E, Blomström-Lundqvist C. A short P-wave duration is associated with incident heart failure in the elderly: a 15 years follow-up cohort study.
J Geriatr Cardiol. 2022 Sep 28;19(9): 643-650.

II. Ostrowska B, Lind L, Sciaraffia E, Blomström-Lundqvist C. Short P-Wave Duration Is Associated with Incident Atrial Fibrillation.
Int Heart J. 2022 Jul 30;63(4):700-707.

III. Lind L, Ostrowska B, Blomström-Lundqvist C. High variability of the R-wave amplitude predicts incident heart failure in the elderly: a cohort study using machine learning.
Submitted to ESC Heart Fail. (open access).

IV. Ostrowska B, Lind L, Blomström-Lundqvist C. An association between heart rate variability and incident heart failure in an elderly cohort.
Submitted to Clin. Cardiol. (open access).

Contents

Abbreviations

ACC	American College of Cardiology
ACEIs	Angiotensin-converting enzyme inhibitors
AF	Atrial fibrillation
AHA	American Heart Association
ANS	Autonomic nervous system
ARNIs	Angiotensin receptor/neprilysin inhibitors
AUC	Area under the curve
AUROC	Area under the ROC (curve)
BMI	Body mass index
CART	Classification and regression trees
CI	Confidence interval
CIED	Cardiac implantable electronic devices
CRP	C-reactive protein
CRT	Cardiac resynchronization therapy
CV	Cardiovascular
CVD	Cardiovascular disease
ECG	Electrocardiogram
ECHO	Echocardiography
EF	Ejection fraction
ESC	European Society of Cardiology
GBR	Generalized boosted regression trees
HDL	High-density lipoprotein
HF	Heart failure
H-F	High frequency
HFmrEF	HF with mildly reduced ejection fraction
HFpEF	HF with preserved ejection fraction
HFrEF	HF with reduced ejection fraction
HFSA	Heart Failure Society of America
HRV	Heart rate variability
ICD	Implantable cardioverter-defibrillator
ICD-8	International Classification of Diseases, Revision 8
IVRT	Isovolumic relaxation time
KNN	K-nearest neighbor classification
LDL	Low-density lipoprotein
L-F	Low frequency

LL	Lars Lind
LMWH	Low molecular weight heparin
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
Min	Minute
ML	Machine learning
MRAs	Mineralocorticoid receptor antagonists
msec	Millisecond
NA	Not applicable
NNET	Neural network
NYHA	New York Heart Association
Pamp	P-wave amplitude
Pdur	P-wave duration
PIVUS	Prospective Investigation of the Vasculature in Uppsala Seniors
PNS	Parasympathetic nervous system
PR	PR interval on ECG
QoL	Quality of life
QRS	QRS complex on ECG
RCT	Randomized clinical trial
RF	Random forest
ROC	Receiver operating characteristics
RV	Right ventricle
SD	Standard deviation
SGLT2	Sodium-glucose co-transporter 2
SNS	Sympathetic nervous system
SVM	Support vector machines

1 Introduction

Heart failure (HF) is a clinical syndrome, manifested by symptoms attributable to structural or functional cardiac abnormalities[1]. However, a ventricular dysfunction may precede the symptoms of HF and is independently associated with worse outcomes[2,3]. The current European Society of Cardiology (ESC) guidelines stress the importance of identifying, modifying or treating risk factors for HF such as diabetes, hypertension, metabolic syndrome, sleep apnea, arrhythmias, coronary disease, sedentary habits, smoking and alcohol abuse to prevent or delay the onset of HF[1]. Moreover, the AHA/ACC/HFSA guidelines recognize patients at risk of HF as "stage A" recommending a healthy lifestyle and a natriuretic peptide biomarker-based screening followed by multidisciplinary care for these patients. The same guidelines recommend an application of validated HF prediction models for the general population[4]. However, it is challenging to identify asymptomatic individuals without risk factors and still being at risk of developing HF.

Atrial fibrillation (AF) is another epidemic disease and the most common arrhythmia, related to a many pathophysiological conditions and conferring an increased risk of HF, stroke and mortality[5-7]. The impact of clinical risk factors, including multiple comorbidities, on the lifetime risk of AF suggests that modification and treatment of these risk factors may reduce the incidence of AF[8,9]. Therefore, a reliable long-term prediction of AF is crucial for improving outcomes.

Abnormalities in atrial structure and function, known as atrial cardiomyopathy, increase the risk of AF and other cardiovascular (CV) events independently of AF[10]. Because AF and HF often coexist and share many risk factors, electrocardiogram (ECG) changes reflecting atrial abnormalities may prove useful in predicting incident AF and HF. ECG is a simple and easily available clinical tool, potentially useful for the wide screening of these diseases.

2 Background

2.1 Heart failure

2.1.1 Epidemiology

Heart failure is one of the main public health problems with a prevalence of approximately 1–2% in the adult population in developed countries[11]. The overall incidence of HF in adults is estimated to be 5/1000 person-years and is still increasing despite recent diagnostic and therapeutic advances[12]. One in five individuals is estimated to develop HF in their lifetime starting at 40 years[13]. Among all HF patients, approximately 84% have reduced left ventricular ejection fraction (LVEF<50%) and 16% have preserved LVEF ≥50%[1]. The prognosis of HF remains poor, with a 5-year mortality rate reaching up to 67%[14.] The hospitalization rate is estimated to be at least 1 per patient-year[15] and is expected to increase even further, mainly due to the progressive ageing of the population[16]. The quality of life (QoL) in HF patients is reduced more than in many other chronic diseases[16]. Moreover, the economic burden of HF is estimated to be 1–2% of the total health care cost in industrialized countries[17].

2.1.2 Pathophysiology and aetiology

Heart failure is a complex clinical syndrome with different aetiologies. It is often an end-stage of many heart diseases (e.g. ischaemic, valvular, congenital or arrhythmic). Other less common causes of HF are: alcohol, toxins, cardiotoxic drugs, myocarditis, cardiac infiltrative diseases (amyloidosis, sarcoidosis), storage disorders, pericardial/endomyocardial diseases, metabolic disorders and neuromuscular diseases[1]. Hypertension, diabetes, sedentary, hyperlipidemia, smoking and obesity may contribute to development of HF and are known as traditional risk factors[11]. The aetiology of HF is geography-related with ischaemic heart disease and hypertension being the main causes of HF in Western Europe and other developed countries[18].

Heart failure is considered a disease with an autonomic imbalance[19]. The persistent activation of the sympathetic nervous system (SNS) leads to a subsequent downregulation of beta-receptors, which, initially a compensatory mechanism to the haemodynamic changes in HF, contributes to further deterioration in the pump function and maladaptive cardiac remodelling[20,21]. High

sympathetic activity in HF patients has been associated with a worse prognosis, increased mortality and decreased functional capacity[22]. Beat-to-beat heart rate variability (HRV), based on the fluctuation in the time intervals between adjacent heartbeats, is a simple, non-invasive assessment of the autonomic function[23].

Systemic inflammation has been recognized as a pathophysiological mechanism and a contributor to the progression of all types of HF[24,25]. Elevated levels of C-reactive protein (CRP), a widely used marker of inflammation, are highly prevalent in HF patients regardless of the HF type[25]. The autonomic nervous system (ANS) is largely involved in regulating the inflammatory process[20]. Whereas the parasympathetic nervous system (PNS) is mainly responsible for anti-inflammatory regulations, a predominance of SNS activity is associated with increased inflammation[20].

2.1.3 Diagnosis and classification

Heart failure is a clinical syndrome consisting of typical symptoms (breathlessness, fatigue, swelling) and structural/functional cardiac abnormalities. The very first presentation of HF is called incident or de novo HF[26]. The fundamental mechanism of HF is tissue congestion caused by fluid retention due to myocardial dysfunction associated with renal and vascular dysfunction. Pulmonary congestion results in increased pulmonary vein pressure with subsequent alveolar and interstitial oedema, manifesting as dyspnoea. The systemic congestion results in jugular vein distension, peripheral oedema and weight gain[27]. Because symptoms and clinical signs alone are unspecific, objective evidence of myocardial dysfunction is required for making the diagnosis of HF. A diagnostic algorithm combining symptoms, signs, risk factors, ECG, echocardiography (ECHO) and levels of B-type natriuretic peptide has been published in recent ESC guidelines[1].

The traditional classification of HF is based on LVEF measured by ECHO. The current ESC classification divides HF into three groups[1]:

- HFrEF= HF with reduced ejection fraction (LVEF≤40%)
- HFmrEF=HF with mildly reduced ejection fraction (LVEF 41-49%)
- HFpEF= HF with preserved ejection fraction (LVEF≥50%).

Right ventricular (RV) HF (RV-HF) secondary to LV-HF is common and contributes to poor prognosis[28]. Isolated RV-HF due to a primary RV disease is its own entity[28]. Another commonly used classification of HF is based on the severity of symptoms and is called the New York Heart Association classification (NYHA I-IV). NYHA class I defines the stage without limitation of ordinary physical activity, whereas NYHA class IV denotes symptoms at rest or any physical activity. NYHA class II and III are stages with slight and

marked limitations of physical activity, respectively[29]. Current ACC/AHA classification categorizes HF into Stages A–D, emphasizing the process of development and progression of HF. As opposed to the ESC guidelines, this classification includes stage A, defined as "at risk for HF," based on the presence of risk factors alone[4]. Heart failure may also be classified according to its aetiology[29].

2.1.4 Treatment

There are three main goals of HF treatment [1,4]:

- reduction in mortality
- reduction in HF hospitalization rate
- improvement in QoL and functional capacity

The cornerstone of treatment of HFrEF/HFmrEF is pharmacotherapy with four main groups of drugs[1]:

- angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor/neprilysin inhibitors (ARNIs)
- mineralocorticoid receptor antagonists (MRAs)
- beta-blockers
- sodium-glucose co-transporter 2 (SGLT2) inhibitors

However, treatment of HFpEF is more challenging[30]. Drugs with efficacy for HF with reduced EF, except for SGLT2 inhibitors, have failed to improve mortality or combine outcomes (mortality and hospitalization rate) in HFpEF[31]. In HF patients with LVEF≤35% and a QRS complex duration ≥130 milliseconds (msec), device treatment with pacemakers (cardiac resynchronization therapy [CRT-P]) or defibrillators (CRT-D) has shown a reduction in morbidity and mortality[32], improvement of cardiac function and increased QoL[33]. The risk of sudden death is increased in HF; therefore, treatment with implantable cardioverter-defibrillator as primary prophylaxis is recommended in patients with LVEF≤35%, NYHA class II-III and a narrow QRS-complex or in patients with an arrhythmogenic aetiology of HF[34,35]. ICD is also recommended as secondary prophylaxis in survivors of sudden cardiac death or in symptomatic sustained ventricular arrhythmias[1]. However, the benefit of the device therapy may be offset by serious per- and post-procedural complications, which are probably more frequent than generally acknowledged[36,37].

The current ESC guidelines stress the importance of multidisciplinary management of HF patients, including pharmacological treatment, treatment of risk factors, proper patient education and suitable follow-up[1]. The ACC/AHA statement on the primary prevention of HF emphasizes the importance of a team-based, individualized care approach and lifestyle modification[38].

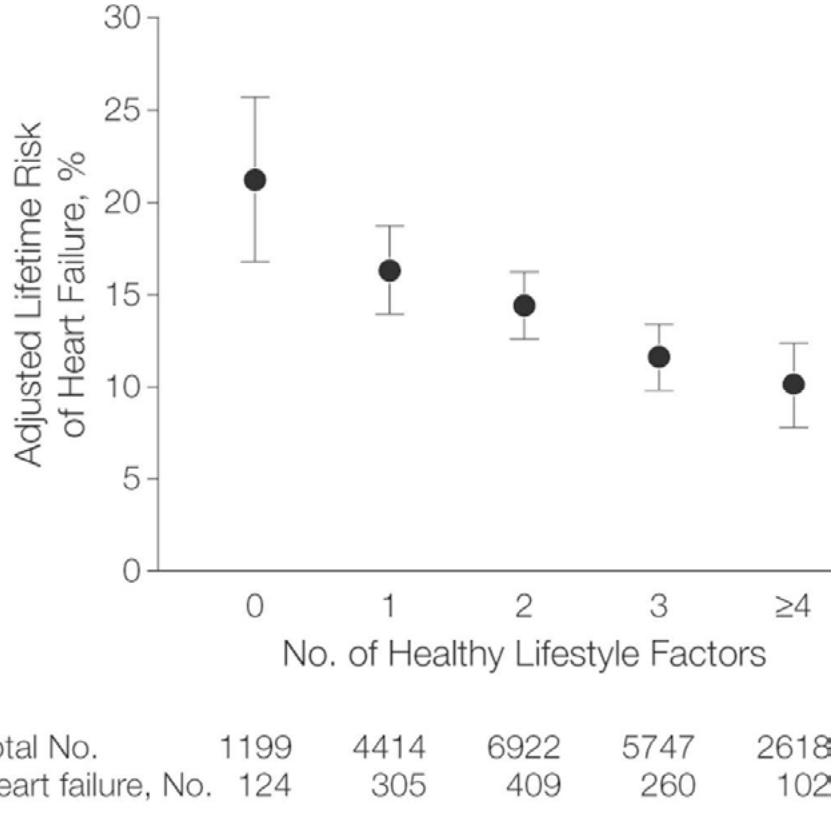

Figure 1. Lifetime risk of heart failure according to number of healthy lifestyle factors

Healthy lifestyle factors: not smoking, maintaining a healthy weight, performing regular exercise, and maintaining a healthy diet.

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2.1.5 Risk stratification for incident heart failure

Early identification of individuals at high risk of HF currently relies on traditional risk factors, including age, sex, systolic blood pressure, hypertension, smoking, diabetes, body mass index (BMI), cholesterol levels, coronary artery disease, prior MI and AF, as well as other risk factors such as sedentary habits or alcohol misuse[39,40]. However, identifying individuals without risk factors still at risk of developing HF may contribute to targeting and optimizing the preventive measures.

Various HF prediction models combining multiple variables have been published in recent years, many based on machine learning (ML) methods[41-43]. More than 50 candidate predictors of incident HF have been proposed, including traditional risk factors, biomarkers, heart rate and AF[44]. Some studies have reported an association between incident HF and ECG abnormalities in

adults such as prolonged QRS duration, LV hypertrophy, ST-T changes and atrial flutter/fibrillation[45-49]. However, studies analyzing the value of adding resting ECG variables to existing CV risk prediction models reported only a small performance improvement, translating to a 0.1-5% increase in the area under the receiver operating characteristic (AUROC) curve or C-statistic[45,50]. To our knowledge, none of the prediction models for incident HF has included ECG indices reflecting the atrial electrical activity.

The P-wave on the surface ECG reflects atrial depolarization. While a normal value of the P-wave duration (Pdur) has not been standardized, an upper cut-off of 110 or 120 msec has been proposed[51,52]. A prolonged P-wave duration (Pdur) is caused by an increased atrial conduction time due to atrial enlargement or fibrosis and has been independently associated with AF, ischaemic stroke and higher mortality[53]. Although a correlation between a prolonged Pdur ≥100 msec and advanced HF has been reported[54], its correlation with incident HF is unclear. A prolonged PR-interval >200 msec is uncommon (0.5-2%) in the healthy population[55] but prevalent (18-52%) in patients with HF[56]. A prolonged PR-interval shortens the effective left ventricular (LV) diastolic filling time, resulting in a reduced preload and an impaired cardiac output[57]. Although PR prolongation has not been associated with increased CV mortality in a healthy population[58], it has been reported to increase the risk of HF and AF in individuals with prevalent CV disease and the elderly[57] .

In the early stages of HF, an overactivity of the ANS has been found[59]. Heart rate variability (HRV) is an accepted indicator of ANS activity. However, data regarding a correlation between HRV indices and incident HF are scarce[60-62].

The ECG is a simple and easily available diagnostic tool; however, its utility for screening for HF or CV diseases is not determined[1] or controversial[50], respectively.

In summary, most of the published and currently used prediction models for incident HF have been unreliable, and only a few have been clinically validated despite their sufficient discriminative ability, defined as the concordance statistic (C-statistic) > 0.70[44]. Therefore, developing and refining the HF prediction models to optimize HF management is important.

2.2 Atrial fibrillation

2.2.1 Epidemiology

Atrial fibrillation is the most common arrhythmia in adults, with a prevalence between 2 and 4%[63]. However, an underestimation of the prevalence is likely given that 10-40% of AF patients have asymptomatic AF episodes[64,65]. Incidence of AF increases with age, and 1 in 3 individuals of European ancestry is expected to develop AF during their lifetime, starting at 55 years of age[66].

Figure 2. Lifetime risk of atrial fibrillation

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Patients with AF have a two-fold increased hospitalization rate and run a 2-3-fold higher risk of CV mortality, a five-fold higher risk of stroke and an increased risk (hazard ratio [HR]=1.4-1.6) of dementia compared to patients free from AF[67,68]. Over 60% of AF patients have impaired QoL and up to 20% suffer from depression[68].

Atrial fibrillation and HF frequently coexist and have common antecedent risk factors[69]. Atrial fibrillation per se confers a three-fold increased risk of HF[67] due to a loss of atrial contractions, irregular and high ventricular rate, ionic remodelling and neurohormonal dysregulation. Similarly, HF promotes the development of AF due to increased ventricular filling pressure, causing atrial dilatation, fibrosis and remodelling[69]. In patients with HF, the overall prevalence of AF ranges between 13% and 27%, increasing with higher NYHA class up to 50% in HYHA class IV[70,71]. Among patients with HFpEF, the prevalence of AF is particularly high, ranging from 30-50%[72]. Moreover, the combination of AF and HF is associated with a worse prognosis and higher mortality rate compared to either disease alone[71,72].

2.2.2 Pathophysiology and aetiology

Atrial fibrillation is characterized by chaotic and rapid electrical activity in the atria. The main concept of AF origin is reentry mediated by a combination of an electric trigger with an electrophysiologic substrate created by an altered refractory period and abnormal conduction velocity. Further development of the substrate results in atrial remodelling with enlargement and fibrosis, which facilitates the occurrence of new AF episodes and, finally, maintenance of the arrhythmia (thus, "AF begets AF")[68,73,74]. Several factors (e.g., ageing, hypertension, metabolic syndrome, thyrotoxicosis, heart failure, alcohol or sedentary life) promote the development of AF mainly through their profibrotic or proinflammatory effects on the atria[75].

2.2.3 Diagnosis and classification

A single-lead surface ECG tracing showing AF with a duration of ≥30 seconds or an entire (10 seconds) 12-lead ECG recording of AF is required for the diagnosis of clinical AF[68]. The most commonly used classification is based on AF presentation, duration and management[68]:

- First diagnosed
- Paroxysmal (duration ≤7 days)
- Persistent (duration >7days and ≤12 months)
- Long-standing persistent (duration >12 months, but not yet accepted as permanent)
- Permanent (no further attempts to restore sinus rhythm)

Other classifications are based either on the aetiology of AF or the severity of the symptoms[76]. The latest North American guidelines include stage 1 ("at risk for AF") and stage 2 ("pre-AF") in their 4-stage AF classification, emphasizing the progressive character of the disease[77]. Given the complexity of AF itself and factors relevant to its management and treatment, ESC guidelines have proposed a novel, structured characterization of AF called 4S scheme[68] based on four domains:

- Stroke risk scores
- Symptom severity
- Severity of AF burden
- Substrate severity

Various classifications related to these domains can be included in this 4S-scheme, which can potentially become a powerful tool for improving the prognosis of AF patients[78].

Atrial fibrillation is a progressive disease characterized by a transition from paroxysmal to non-paroxysmal or from subclinical to clinical forms with an

annual rate of 1-15%[68]. The progression to persistent or permanent AF is related to worse clinical outcomes[79] and higher mortality[80].

2.2.4 Treatment

The three cornerstones of AF treatment are[76]:

- Prevention of thromboembolism (using oral anticoagulants, heparin or low-molecular-weight heparin; left atrial appendage occlusion/exclusion)
- Rhythm control (restoration and maintenance of sinus rhythm with drugs, direct cardioversion, catheter ablation or surgery)
- Ventricular rate control (pharmacological or by atrioventricular node ablation and pacing)

The latest ESC guidelines punctuate the importance of multidisciplinary AF management based on the specific needs and risk profile of an individual patient[68]. A holistic approach to management of AF is summarized as the AF Better Care (ABC) pathway[68]:

- A: Avoid stroke (anticoagulation)
- B: Better symptom control (rate- or rhythm control)
- C: Comorbidity and CV risk factor management, including lifestyle modification

In the North American AF guidelines, a similar therapeutic approach with 3 goals of therapy is defined as SOS (**S**troke risk assessment and treatment, **O**ptimizing all modifiable risk factors, and **S**ymptom management)[81].

In summary, the treatment of risk factors, including hypertension, diabetes, obesity, smoking, alcohol use, hyperlipidaemia, obstructive sleep apnoea and physical inactivity, should be in focus at all stages of AF[68]. Because adherence to treatment is crucial, educating the patients and health care professionals is underlined.

Although AF is thought to be caused by a chronic systemic inflammation[82], trials with statins and fish oil seeking to suppress the inflammation have yielded controversial results. Thus, ESC guidelines do not recommend these drugs as the primary prevention of AF[68].

2.2.5 Risk stratification for incident atrial fibrillation

An asymptomatic AF, occurring in about one third of AF patients[65], may confer a higher risk of stroke and mortality compared to symptomatic AF[83]. However, an unselective screening by heart rhythm monitoring will likely detect only a small proportion of AF cases in the population[84] and the evidence for benefits of such a screening is still lacking[85]. An efficient and cost-effective

AF screening should therefore be targeted at high-risk groups[86,87]. An age-based community screening for incident AF is considered cost-effective[88]. ESC guidelines recommend a systematic AF screening by rhythm monitoring in individuals at high risk of stroke or aged ≥ 75 years and an opportunistic ECG screening in patients aged 65-74 years[68]. However, a screening strategy based on multivariable risk prediction models has been more efficient than one based on age criterion alone[89,90]. In evaluating 14 prediction models for incident AF, the best-performing ones could predict almost four-fold more AF by selective screening of risk individuals compared to general screening of the population[86]. Most AF prediction models have used conventional risk factors and biomarkers as variables while only a few have used ECG variables[89]. Nonetheless, a host of ECG variables, mainly P-wave indices, have been significantly associated with incident AF, including:

- Prolonged P-dur[74,91,92]
- Short P-dur ≤89 msec[74]
- P-wave terminal force in lead V1[92,93]
- Abnormal P-wave axis (any value outside 0-75°)[94]
- P-wave morphology in limb leads[95]
- P-wave dispersion [96,97]
- Prolonged PR-interval[58,98]
- Left atrial enlargement, left ventricular hypertrophy, atrial and ventricular extrasystole[99].
- Decreased HRV, increased and decreased heart rate[100].

Adding selected ECG variables associated with incident AF to traditional risk factors and biomarkers has been evaluated for a few prediction models concerning predictive performance. However, the contribution of ECG variables toward predictive AF discrimination has been absent or limited[92,99,101], although a few studies found a significant improvement in C-statistic by 0.02-0.021[94,102].

As opposed to routine statistical modelling, ML methods have the potential to offer the ECG a higher utility for the prediction of incident AF. ML has identified with high accuracy previous AF episodes from a single sinus rhythm ECG recording[103]. ECG is an available and easily accessible tool in primary care settings and may prove useful for creating reliable AF prediction models in the future.

A highly performing prediction model may also prevent the development of AF because early identification of individuals at risk of AF and treating or modifying risk factors may hinder the development of atrial remodelling[68].

2.3 Electrocardiography

The 12-lead ECG is among the most frequently used clinical tools in cardiology. This technique is thanks to Willem Einthoven, "the father" of the ECG, who first used a galvanometer to register cardiac electrical signals and published his observations at the beginning of the 20th century. Sir Thomas Lewis was the first to apply ECG in clinical practice in 1909 by describing ECG changes in AF[104]. ECG was introduced in cardiac intensive care for the first time in the 1960s.

ECG tracing showing AF is a requirement for its diagnosis[68]. However, an HF diagnosis is complex and sometimes challenging. Thus, attempts have been made to find ECG changes specific to this disease. In the 1980s, Goldberger published a report on a "triad" of ECG changes related to HF, including a high QRS amplitude and poor R wave progression in the precordial leads combined with low QRS amplitude in limb leads. However, larger studies found a low specificity of Goldberger´s HF criteria[104]. The specific ECG pattern for HF has not yet been defined.

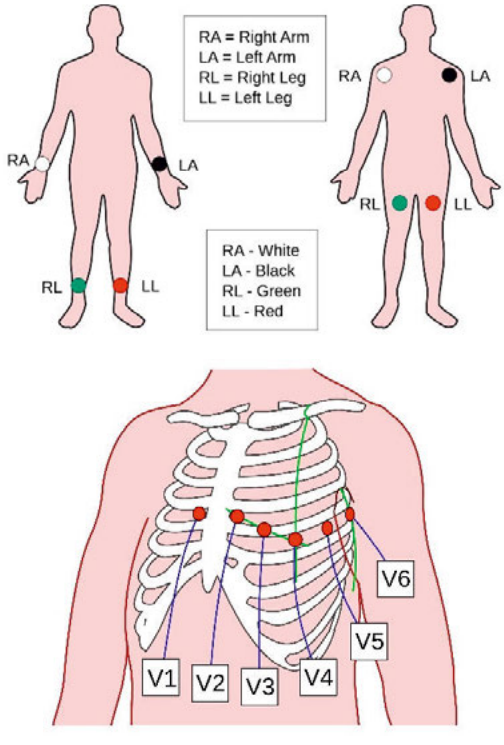

Figure 3. Placement of 12-lead ECG.Leads: V1-V6 - precordial (chest) and unipolar; I-III- limb and bipolar; aVR/aVL/aVF- augmented and unipolar

Downloaded from Wikimedia: (https://commons.wikimedia.org/wiki/File:Precordial_Leads_2.svg;https://commons.wikimedia.org/wiki/File:Limb_leads_2_ENG.svg).

Despite progress in cardiac genetics and advanced cardiac diagnostics, ECG remains a widespread and important tool in daily clinical practice.

3 Aims

The overall aim of this thesis was to find ECG-derived variables suitable for the prediction of incident HF and AF, focusing on cardiac conduction and HRV. The main research questions were to assess whether:

Paper I	Pdur and PR-interval duration were associated with incident HF
Paper II	Pdur and PR-interval duration were associated with incident AF
Paper III	An addition of ECG variables selected by ML to traditional risk factors improved the performance of the conventional HF prediction model
Paper IV	L-F/H-F ratio, a frequency-domain HRV index, was related to incident HF and whether the addition of the L-F/H-F ratio to traditional risk factors improved the performance of the conventional HF prediction model

4 Methods

4.1 Study population

4.1.1 Paper I-IV

All four studies were based on the PIVUS (Prospective Investigation of the Vasculature in Uppsala Seniors) study, which, in 2001, invited all individuals aged 70 years from Uppsala, Sweden, to participate[105]. Of 2025 invited subjects, 1016 (50%) agreed to participate. All participants gave their written informed consent. The PIVUS study was approved by the Research Ethics Committee of Uppsala University and conformed with the principles outlined in the Declaration of Helsinki (published in Br Med J 1964).

4.2 Design

4.2.1 Paper I, III and IV

The population of three studies (I, III and IV) was retrospectively included from the PIVUS study after excluding those with prevalent HF, implanted pacemaker/defibrillator, atrial tachyarrhythmias, second- and third-degree atrioventricular block, delta waves and a QRS complex duration ≥130 msec at baseline, leaving 836 of 1016 (82%) individuals for evaluation. Data on HF, AF and myocardial infarction (MI) diagnoses were retrieved from the Swedish Cause of Death Register and the Swedish Hospital Discharge Register and validated by an experienced clinician (LL). At baseline, a medical history with medications was registered and a CV examination, including blood pressure, ECG, ECHO and blood sampling in the fasting state, was performed. A six-lead ECG (V1 through V6) was recorded digitally for 5 minutes (min) with a sampling frequency of 500Hz and during controlled breathing at a rate of 12/min. Coffee and smoking were not allowed on the same day. A semiautomatic software EClysis (AstraZeneca R&D, Molndal, Sweden) was used to analyze baseline ECGs[106,107]. Data on RR-intervals were collected and an analysis of HVR in the frequency domain was performed. M-mode echocardiography was used to measure LA and LV dimensions and calculate LV mass index, LV volume, stroke volume and LVEF. The LV diastolic filling pattern

was obtained with a pulsed Doppler. Baseline characteristics of the 836 participants are shown in Table 1.

A re-examination of the PIVUS study participants was conducted after 5 and 10 years with a similar design as at baseline except for the ECG, which was used to record AF only. The follow-up of the PIVUS study population was 15 years.

Table 1. Baseline characteristics in 836 individuals

Variables	Values
Female sex, n (%)	418(50)
Smoker, n (%)	11(1.3)
BMI (kg/m^2)	27 (4.2)
Beta-blockers therapy, n (%)	15 (1.8)
Systolic blood pressure (mmHg)	150 (22)
Use of antihypertensive treatment, n (%)	30 (3.5)
Diabetes, n (%)	11 (1.3)
AF, n (%)	71 (8.5)
MI, n (%)	92 (11)
LVEF (%)	67 (6)
CRP (mg/l)	2.4 (5.1)
LDL (mmol/l)	3.4 (0.9)
HDL (mmol/l)	1.5 (0.4)
RR-interval (msec)	980 (136)
L-F ($msec^2$) (median, IQR)	1667 (425, 4474)
H-F ($msec^2$) (median, IQR)	146 (65, 303)
L-F/H-F ratio (median, IQR)	13.6 (3.2, 31.3)
Pdur in V1 (msec)	71.3 (20.9)
SD Ramp in V1 (mV) (median, IQR)	0.01 (0.006, 0.013)

Figures are means + one standard deviation (SD) unless otherwise stated.

BMI=body mass index; AF=atrial fibrillation (occurring between baseline and HF diagnosis); HF=heart failure; MI=myocardial infarction (occurring between baseline and HF diagnosis); LVEF=left ventricular ejection fraction; CRP=C-reactive protein; LDL= low-density lipoproteins; HDL= high-density lipoproteins; L-F=low frequency; msec2= millisecond squared; IQR=interquartile range; H-F=high frequency; Pdur=P-wave duration; SD=standard deviation; Ramp=R-wave amplitude; mV=millivolt

4.2.2 Paper II

The target population in study II consisted of subjects included in the PIVUS study after excluding those with rhythms other than sinus on baseline ECG, second- or third-degree atrioventricular block, delta waves, prevalent AF, history of AF and a permanent pacemaker/defibrillator. After meeting the exclusion criteria, 877 individuals were enrolled for further analyses.

4.3 Statistical methods

A p-value < 0.05 was considered significant for all studies (I-IV). STATA16 (Stata Inc., College Station, TX) was used for the calculations. R 4.0.4 for Mac OS X was used for the ML application (Paper III), mainly using the caret package.

Traditional risk factors for HF were sex, systolic blood pressure, use of antihypertensive treatment, smoking and BMI. Diabetes, LDL- and HDL-cholesterol were not related to incident HF in the initial models regarding confounders. Age was the same for all participants.

4.3.1 Paper I

Cox proportional-hazard analysis assessed the relationship between the Pdur and PR interval duration as independent variables and incident HF as outcome. The ECG variables were modelled as restricted cubic spline functions with three knots (10th, 50th and 90th percentiles) due to an assumption of non-linear relationships.

Adjustment was performed for the traditional risk factors. C-statistic based on logistic regression was used to evaluate the performance of the HF prediction models. After excluding major non-linear relationships between ECG- and ECHO variables, linear regression models were performed between the ECG- and ECHO variables with adjustment for sex, inter-beat (RR) interval, beta-blocking agents, systolic blood pressure, BMI and smoking (age same in all participants).

4.3.2 Paper II

Cox proportional-hazards analysis assessed the relationship between the Pdur and PR interval duration as independent variables and incident AF as outcome. Adjustment was performed for traditional risk factors for AF such as systolic blood pressure, smoking, BMI, HF diagnosis prior to AF diagnosis (n = 78), the RR-interval and use of beta-blocking agents. Diabetes, LDL-, and HDL-cholesterol were not included as traditional risk factors, as they were not significantly related to incident AF in the present sample. C-statistic based on

logistic regression was used to evaluate any improvement in AF discrimination after the selected ECG variables were added to the traditional risk factors for AF.

4.3.3 Paper III

This analysis applied an AUROC curve to measure the models' predictive performance. EGC variables in 6 leads, 134 variables in total, were inverse rank transformed and a restricted cubic spline function with three knots (10th, 50th and 90th percentile) was created for each variable.

A training dataset with a random sample of 70% of the PIVUS cohort and a testing dataset with the remaining 30% of the cohort were created. Incident HF was the outcome and the independent variables were sex (age same in all participants) and the spline functions of the ECG variables. A cross-validation of the model performance in the training dataset for six different ML models was then made and the model with the best accuracy was chosen.

A logistic regression model was applied first to the training dataset and in the next step, to the testing dataset with incident HF as outcome and traditional risk factors as covariates. Only covariates with $p<0.05$ were used further in the testing dataset.

In the next step, logistic regression was performed in the testing dataset using incident HF as the outcome variable, previously selected ECG variables of greatest importance and traditional risk factors as covariates. The performance of this model was then compared to the performance of the model with traditional risk factors alone as independent variables.

Moreover, the top ECG variable was tested against ECHO variables using linear regression models adjusted for sex and traditional risk factors. All variables were inverse rank transformed. Finally, a correlation between the top ECG variable and the L-F/H-F ratio was assessed using a linear regression model with adjustment for sex.

4.3.4 Paper IV

Cox proportional-hazards analysis assessed the relationship between the L-F/H-F ratio as independent variable and incident HF as outcome. Adjustment was performed for traditional risk factors. Due to a theoretical possibility of a non-linear relationship, the L-H/F-H ratio was modelled as a restricted cubic spline function with three knots (10th, 50th and 90th percentile).

After that, relationships between L-F power and the H-F power as independent variables and incident HF were assessed in two models using the same confounders as mentioned above.

C-statistic based on logistic regression was used to evaluate any improvement in HF discrimination after adding the L-F/H-F ratio to the traditional risk factors. In the next step, C-statistic based on logistic regression was employed

to evaluate any improvement in HF discrimination after adding the L-F/H-F ratio along with Pdur in lead V1 and SD Ramp in lead V1 to the HF traditional risk factors. All analyses were repeated with additional adjustments for AF and MI occurring between the baseline and HF diagnosis.

The pairwise associations between L-F/H-F ratio and the two ECG variables: Pdur in lead V1 and SD Ramp in lead V1 were analyzed using Spearman´s correlation method. Finally, the pairwise correlations between the baseline level of the inflammatory marker CRP and the three variables: L-F/H-F ratio, Pdur in lead V1 and SD Ramp in lead V1 were tested using Spearman´s correlation.

5 Results

During the 15-year follow-up, 107/836 (12,8%) participants were diagnosed with HF, giving an incidence of 9.8/1000 person-years. Some, 222 individuals died during the follow-up (18 deaths due to HF) (Paper I, II-IV).

During 15 years of follow-up, 189/877 (21,5%) individuals were diagnosed with a new-onset AF, giving an incidence of 17.6/1000 person-years (Paper II).

5.1 Paper I

The Pdur in V1 was significantly associated with incident HF after adjustment for traditional risk factors ($p<0.0001$). The relationship was U-shaped ($p=0.0006$ for non-linearity), with the lowest risk seen at a Pdur of 80 msec, which became a significantly increased risk at Pdur < 60 msec (Figure 4).

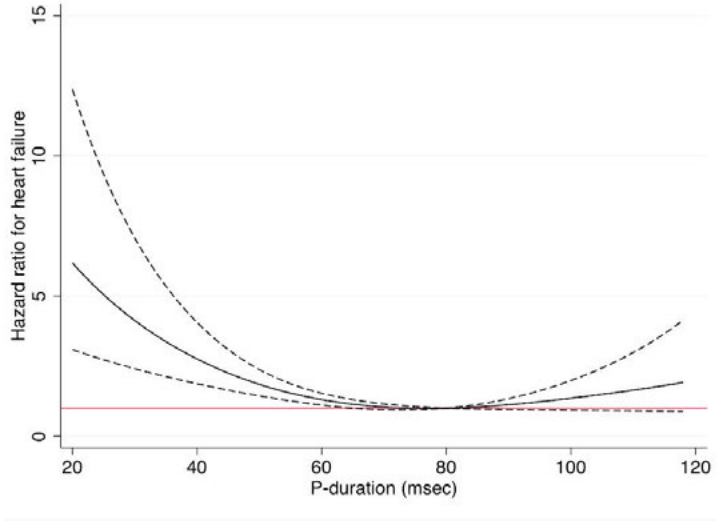

Figure 4. Relationship between P-wave duration in lead V1 and incident heart failure.

The solid line represents the hazard ratio for incident heart failure. The dashed line represents the 95% confidence interval.

A Pdur of 40 msec had an HR of 2.75 [95% confidence interval (CI) 1.87-4.06]. Long Pdur values did not reach statistical significance [HR 1.35 (95% CI 0.92-1.99) for Pdur at 100 msec]. A similar U-shaped association was also seen between Pdur in V3 and incident HF. A short Pdur (<60 msec) improved the discrimination of future HF by 3.6% when added to the model with traditional risk factors [AUROC curve 0.690 (95%CI 0.635-0.744) vs AUROC curve 0.727 (95%CI 0.677-0.776) when including Pdur, p=0.048]. The Pdur in V1 significantly correlated with LA diameter, LVEDD and LV mass. There was no association between the PR-interval in V1 and incident HF (p=0.15).

5.2 Paper II

The Pdur (in lead V1) showed a significant relationship with incident AF (p=0.017) when adjusted for sex only (Figure 5). This relationship was unaffected by adjustments for traditional risk factors for AF (p = 0.017 for Pdur after multiple adjustments). At Pdur=42 msec (10th percentile of the distribution), the risk estimate was 1.55 (95% CI 1.15–2.09). A long Pdur might also confer a risk, but this tendency was not significant. Adding a short Pdur (≤ 60 msec) to the traditional risk factors did not improve the discrimination of AF. There was no association between the PR-interval in V1 and incident AF.

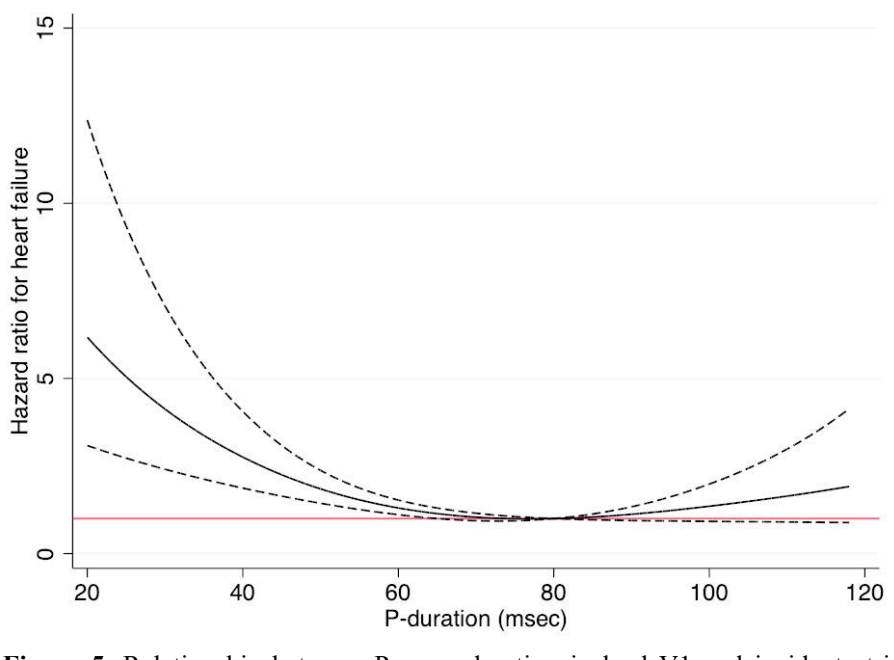

Figure 5. Relationship between P-wave duration in lead V1 and incident atrial fibrillation.
The solid line represents the hazard ratio for incident heart failure. The dashed line represents the 95% confidence interval.

5.3 Paper III

Of the six ML models in the training dataset, the random forest (RF) model produced the highest AUROC curve for predicting incident HF based on ECG variables. Of the 18 top ECG variables selected by the RF algorithm (Figure 6), the eight most important resulted in an AUROC curve of 0.774 (95%CI 0.696-0.851).

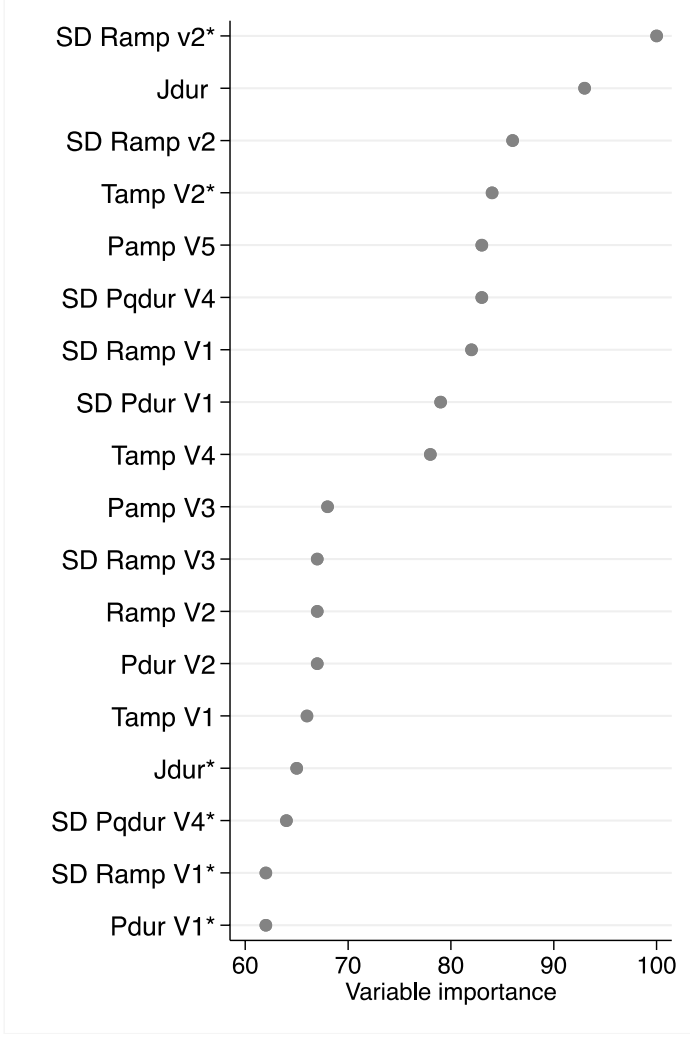

Figure 6. Top-ranked ECG variables in the random forest model for incident heart failure in the training dataset
*denotes the non-linear part of the spline model. Due to the limited number of cases in the testing data set, only 8 of the 18 top-ranked variables were used for further analysis. Note the different results for the linear and non-linear spline of the variable.
SD=standard deviation; P, R, q, T, J=waves on ECG, amp=amplitude; dur=duration (Jdur is measured in V1)

Smoking, prior MI, AF before HF diagnosis and BMI were the only significant traditional risk factors selected in the training dataset and were used in the testing dataset in a logistic regression model, resulting in an AUROC curve of 0.720 (95% CI 0.625-0.813). The further addition of the eight most important ECG variables to this model resulted in an AUROC curve of 0.8370 (95% CI 0.775-0.898) which was an improvement by 11.7% (p=0.0043 for difference) (Figure 7).

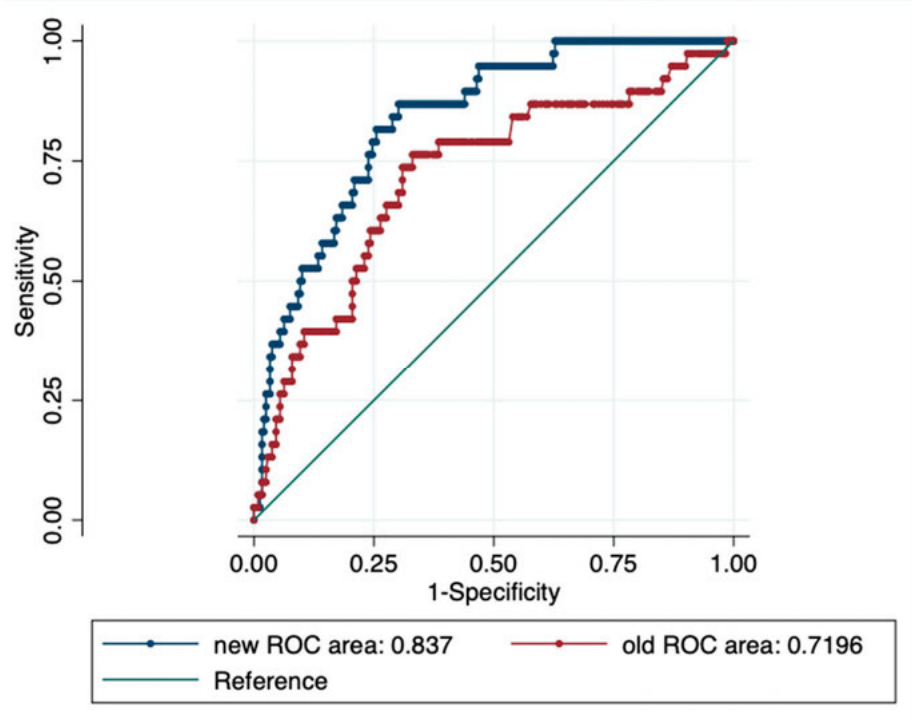

Figure 7. Receiver operating characteristics (ROC) curves for two models

"old" denotes a logistic regression model including traditional risk factors for heart failure; "new" denotes a logistic regression model including traditional risk factors for heart failure plus eight selected ECG variables, p=0.0043 for the difference between "old" and "new." Note the improved performance of the prediction model after adding the selected ECG variables to the traditional risk factors

The most powerful predictive ECG parameter was the beat-to-beat variation (SD) of the R amplitude (Ramp) in V1 giving an odds ratio of 2.26 (95% CI 1.4-3.65). There were no significant relationships between the SD of the Ramp in V1 and any of the ECHO variables except for interventricular septum thickness.

5.4 Paper IV

A significant, non-linear, inverse association, driven mainly by a L-F/H-F ratio< 30, was found between the L-F/H-F ratio and incident HF. The association curve was flat for higher levels of the L-F/H-F ratio [HR for the total curve 0.78 (95% CI 0.69-0.88), p<0.001] (Figure 8). An L-F/H-F ratio of =10 resulted in an HR 2.0. The relationship between the L-F/H-F ratio and incident HF was mainly due to the relationship between L-F and incident HF [HR 0.78 (95% CI 0.69-0.87), p<0.001], as H-F was not significantly related to incident HF [HR 0.96 (95% CI 0.82-1.13), p=0.65].

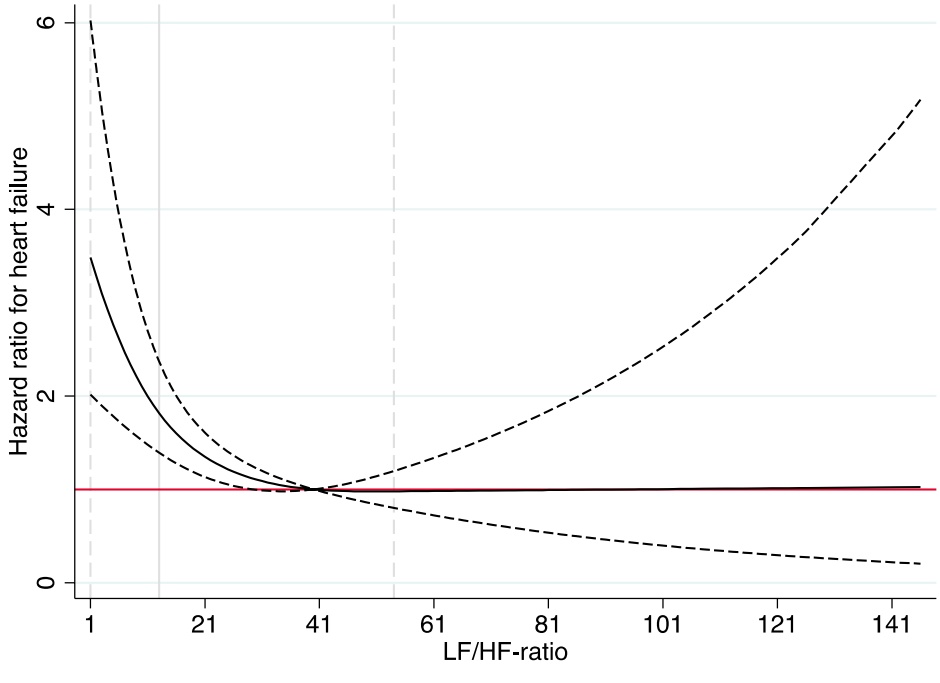

Figure 8. Relationship between L-F/H-F ratio and incident heart failure

The solid line represents the hazard ratio for incident heart failure. The dashed line represents the 95% confidence interval. The horizontal solid line represents the hazard ratio=1

Both Pdur in V1 and the SD Ramp in V1 2 ECG were significantly associated with incident HF after entering the abovementioned model [a non-linear inverse correlation for the Pdur (p=0.0088) and a linear direct correlation for the SD Ramp (p= 0.0061)]. Compared to the model with the traditional risk factors alone, the addition of the L-F/H-F-ratio improved HF predictive performance by 3.3% (p=0.03) [AUROC curve 0.69 (95% CI 0.63-0.74) vs AUROC curve 0.72 (95% CI 0.67-0.77), respectively].

Compared to the model with traditional risk factors alone, further addition of the Pdur in V1 and SD Ramp in V1 along with the L-F/H-F-ratio resulted in an improvement of 6.1% (p=0.0015) in predictive performance [AUROC curve 0.69 (95% CI 0.63-0.74), AUROC curve 0.75 (95% CI 0.70-0.80), respectively]. There was a weak[108] correlation between the L-H/F-H ratio and Pdur in V1 and between the L-H/F-H ratio and SD Ramp in V1. There was a negligible[108] pairwise correlation between the baseline CRP level and: the L-H/F-H ratio, the Pdur in V1 and SD Ramp in V1, respectively.

6 Discussion

The main finding of this thesis was the importance of ECG for the prediction of incident HF (Paper I, III, IV) and incident AF (Paper II). Although the ECG is a widespread and easily available clinical tool, its utility for screening in primary prevention of HF has gone unrecognized[1,50].

A novel finding was the U-shaped association between the Pdur and incident HF (Paper I). The similar U-shaped association between the Pdur and incident AF, found in study II (Paper II), confirmed to the results of a large Danish population study[74]. The P-wave reflects atrial depolarization and its duration measures the atrial conduction time[109]. The finding of a robust correlation between the short Pdur and incident HF and AF, may have several potential explanations. The Pdur is influenced by the ANS and seems to be shortened by beta-adrenergic stimulation with isoproterenol and prolonged by beta-blockade[110]. However, in our statistical calculations an adjustment was made for the RR-interval and the treatment with beta-blockers, which should have eliminated these confounders. Another cause of the shortening of the Pdur may be an increased atrial conduction velocity, related to changes in transmembrane ion channels or gap junctions. Relaxin, an emerging biomarker in HF, appears to possess the ability to increase the atrial conduction velocity[111-113]. Increased levels of relaxin along with a subsequent downregulation of primary relaxin receptors have been found in patients with prevalent HF[114]. Relaxin is a peptide hormone with anti-inflammatory, anti-fibrotic, anti-hypertrophic and anti-apoptotic effects, exerted on various organs including the myocardium[115]. Because fibrosis is one of the main mechanisms for HF and AF, the enhanced secretion of relaxin may reflect an early profibrotic process in the myocardium before the development of HF and AF. The enhanced velocity of atrial conduction causing the shortening of the Pdur may thus be induced by relaxin. Relaxin has already been described as a novel biomarker for the early detection of MI[116], but it might also prove useful for predicting of incident HF and AF.

Another ECG variable, a high beat-to-beat variation in Ramp, strongly predicted incident HF in study III. Data on the beat-to-beat variation of QRS-amplitude are scarce, but this phenomenon can be explained by the "Brody effect" (theoretical analysis of the influence of left ventricular chamber size on QRS wave amplitude) attributed to alterations in the thoracic electrical conductivity due to changes in left ventricular filling volume[117-119]. A high beat-

to-beat Ramp variation has been associated with a hyperactive sympathetic or hypoactive parasympathetic cardiac modulation in patients with anxiety disorders, ischaemic heart disease and HF[119]. A predominance of sympathetic activity has been generally acknowledged in chronic HF[21]. Given the finding in Study III, it can be hypothesized that an increased sympathetic activity, which increases the Ramp's variation, also precedes HF development. Study III, however, could not determine whether the prevailing mechanism was a hyperactive sympathetic or a hypoactive parasympathetic cardiac modulation, nor could it determine the causality.

Heart failure is considered a disease with an autonomic imbalance[19]. An increased sympathetic drive in patients with manifest HF has been associated with adverse prognosis and lower functional capacity[22]. A simple, non-invasive assessment of the autonomic function is the HRV, which can be measured in time-domain or frequency-domain indices, the latter one assigning bands of high, low or very low frequency (H-F, L-F, VL-F) by power spectral analysis[23]. A decreased HRV in chronic HF is commonly known and associated with adverse outcomes[120]. However, data on the relationship between HRV and incident HF are scarce, although an association between the time-domain HRV indices and incident HF has been described[60,121,122]. As far as we know, the relationship between HRV in the frequency-domain and incident HF is unknown.

The HRV in the frequency-domain provides information about HRV power as a function of frequency: the high frequency (H-F) component is thought to be mediated mainly by the vagal tone and the low frequency (L-F) component by both the sympathetic and vagal tone[123,124]. It has also been suggested that L-F power is mainly a measure of cardiac autonomic modulation by baroreflexes[125]. Although some authors have interpreted an increased L-F power as high sympathetic activity[126], others found an attenuation or absence of the L-F component measured on short-term ECG recordings in patients with severe HF known to have a grossly elevated sympathetic tone[127]. Decreased L-F power in a chronic state of a high sympathetic drive might be due to a down-regulation of the β-adrenoceptors, which limits the responsiveness of the sinus node[127,128]. Other possible explanations for an attenuated L-F component might be an impaired central autonomic modulation and a reduced baroreflex sensitivity[120]. Reduced L-F power in chronic HF patients has been linked to increasing severity of HF and higher risk of sudden death[120,124].

Some authors have considered another HRV index, the LF/HF ratio, to reflect the balance between the SNS and PNS activity[123,129,130]. However, PNS and SNS interactions are complex and interdependent but not necessarily reciprocal or balanced[128], which makes the L-F/H-F ratio difficult to interpret[131]. In clinical studies, low ratio values have been associated with increased lifetime risk for CV disease[19] and hyperglycemia[132].

Study IV (Paper IV) found a strong relationship between a decreased L-F/H-F ratio and incident HF in an elderly population. This finding indicated

an autonomic imbalance prior to the development of HF, consistent with Study III´s results. However, the main mechanism of this finding was unclear, although the concomitant strong correlation between the reduced L-F power and incident HF implied an increased sympathetic activity, possibly due to a decreased baroreceptor sensitivity prior to HF. In chronic HF, high sympathetic tone reduces baroreflex sensitivity, which impairs baroreceptors` ability to restrain SNS activity[133]. However, data on baroreflex sensitivity prior to HF are lacking. Results of Study IV (Paper IV) may well be explained by reduced baroreflex sensitivity due to increased sympathetic tone preceding incident HF. Because the L-F/H-F ratio and the SD of Ramp were statistically uncorrelated, they may be considered independent indices of autonomic dysregulation.

ECG is still the gold standard for HRV measurements[134]. The optimal technique for HRV measurement has not been determined[21], but the frequency-domain technique may be more appropriate for the quantification of HRV compared to the time-domain technique[23,130]. Moreover, the time-domain analysis should be performed from a long-term recording. In contrast, the frequency-domain analysis is preferably performed from a short-term, standardized recording, which is simpler and potentially more applicable in daily clinical practice[135]. Heart rate variability measurement is a non-invasive and inexpensive technique that may prove useful in detecting individuals at risk of HF, which can target and optimize the preventive strategy. Further research should focus on the utility of HRV in prediction models for incident HF and on improving of HRV measurement techniques.

A large number of prediction models for incident HF have been published[41]. The traditional risk factors have been the best predictors of HF[39]. In addition, ECG and echocardiographic parameters including left bundle branch block, ST-segment depression and left ventricular hypertrophy, as well as biomarkers including C-reactive protein, cardiac troponin and N-terminal pro-brain natriuretic peptide, have been proposed as predictors of incident HF[39,47,49,136]. However, adding resting ECG variables to existing CV risk prediction models reported only small improvements in the discrimination capacity resulting in a 0.1-5% increase in the AUROC curve or C-statistic[50]. In Study III, adding eight ECG variables selected by ML to traditional HF risk factors improved the model's predictive performance by 11.7% compared to conventional risk factors alone. This improvement was the largest improvement reported for ECG variables in this setting. In Study IV, the addition of only three variables (L-F/H-F ratio, the Pdur and the SD Ramp in lead V1) to traditional HF risk factors improved the performance of the HF prediction model by 6.1% compared to traditional risk factors alone, which was also a large improvement. In conclusion, the ECG variables may prove useful in predicting incident HF in the future models, the performance of which may be substantially improved by ML methods.

Systemic inflammation has been recognized to be present in HF irrespective of LVEF, correlating with HF severity and prognosis[25]. However, studies

on the correlation between CRP, a commonly used inflammatory marker, and incident HF have shown divergent results[137-140]. Although the inflammatory process and the ANS are interconnected[20], Study IV (Paper IV) found no significant correlation between the baseline level of CRP and the two indicators of the ANS activity: L-F/H-F ratio or the SD Ramp in V1, prior to the development of HF.

7 Limitations and strengths

The main limitation of this thesis is the measurement technique. Because only precordial ECG leads were available at inclusion and the terminal portion of the P-waves was not analyzed separately, it precluded the calculation of P-wave dispersion, P-terminal force in V1 and amplitude of the second negative component of the P-wave. LVEF was determined from the M-mode echocardiographic recordings with the Teicholz formula at baseline, which may overestimate the LVEF[141] and is a less accurate technique than the Simpson or strain echocardiography methods[142]. Moreover, a distinction could not be made between HFrEF and HFpEF, as the diagnosis of HFpEF was unclear at the time of data collection.

At baseline, data on current alcohol consumption only were collected; thus, they were not used in the statistical calculations, which is another limitation. All four analyses were performed on the PIVUS cohort of elderly and mainly ethnically Swedish individuals, requiring caution in generalizing the results.

The major strengths of all four studies are using a digital ECG analysis performed by a validated software, which enabled reproducibility reported for computerized measurements[143] and the complete data set in the PIVUS study. There were ≤1% missing values at baseline managed by listwise deletion instead of imputation. Another strength is the long-term follow-up, longer than in most publications concerning prediction models for incident HF[44] and incident AF[89] that we have identified. Moreover, the outcomes (HF and AF) were validated and the repeated ECG recordings after 5 and 10 years enabled the detection of most AF cases. Although paroxysmal AF, particularly if asymptomatic, may have been underdiagnosed in our cohort, the incidence of AF in study II (17.6/1000 person-years) was comparable with that observed for this age category in a large epidemiological German study (12.5–25.8/1000 person-years), which used in-hospital records and outpatient diagnoses[144].

8 Conclusions

Early identification of individuals at risk of incident HF or AF may target and optimize their prevention and improve outcomes. As a simple and easily available clinical tool, ECG may be useful for this purpose.

In the PIVUS population of elderly individuals, a short P-dur in lead V1 significantly predicted incident HF and incident AF. Two other ECG-based variables, an increased SD of Ramp in lead V1 and a decreased L-F/H-F ratio, markers of the ANS balance, were also strongly related to incident HF indicating an autonomic dysregulation before development of HF. Moreover, adding ECG variables selected by ML methods greatly improved the performance of HF prediction based on traditional risk factors alone.

Although a 5-min ECG is seldom recorded in routine clinical practice, it is a feasible technique that could easily be adopted in primary care settings.

9 Clinical implications and future perspectives

Further development and refinement of risk predictors for incident HF and AF is paramount because HF and AF may be delayed or prevented by modifying and treating risk factors[145]. Early identification of individuals at high risk of HF may improve poor outcomes and reduce national health care costs[1].

Machine learning, a scientific discipline combining statistics and computer science, has emerged as a powerful and promising tool in preventive cardiology[41]. Unlike classical statistics, ML can manage massive amounts of clinical data combined with biometrics, genomics and proteomics. While classical statistics needs to make assumptions before data processing, ML algorithms may work unconditionally on the collected data. Despite the pitfalls and disadvantages of contemporary ML algorithms, it is becoming evident that prediction models built with this technology have the potential to grossly outperform the accuracy of the current prediction models[146,147]. Various ECG-based ML algorithms for predicting incident HF have been adopted in recent years[148]. Novel ECG features and patterns, which are not discernable on the common surface ECG recordings, are being discovered by ML methods using wavelet transformation[149]. ECG has a potential to become an important tool in the HF and AF screening strategy.

Because HF is a heterogeneous syndrome with only partly understood pathophysiological mechanisms, the application of ML algorithms may improve or even thoroughly revise the classification of HF, enabling optimization of its management.

Based on the findings in this thesis, autonomic balance markers may prove useful in predicting incident HF. Dysregulation of the ANS activity is considered involved in the pathogenesis of HF[60,62,150]. Therefore, an early autonomic regulation with neurohormonal blockers or devices may delay or prevent the development of HF[151], but this proposal warrants further research.

Relaxin 2 (RLX-2)-receptors have emerged as a new therapeutic target in the treatment of HF despite contradictory results on the effects of RLX-2 in acute HF[152,153]. However, the need for intravenous administration, short half-life and high costs still limit the clinical utility of RLX-2 in the treatment of HF. Therefore, research to identify novel RLX-2-receptor agonists useful for a simple administration route, is ongoing[154]. Relaxin-2 has also been proposed as a novel CV biomarker[155]. Increased levels of RLX-2 have been linked to

the severity of chronic HF[154] and acute HF[156], as well as inflammation and oxidative stress markers in patients with AF[157]. Higher levels of this hormone have been reported in AF patients compared to patients with sinus rhythm[158]. It is generally accepted that RLX-2 can potentially become a valuable biomarker for risk stratification in patients with prevalent HF or AF[155]. Although studies on association between RLX-2 and incident HF or AF are lacking, RLX-2 may prove useful in screening high-risk individuals.

10 Summary in Swedish (sammanfattning på svenska)

Hjärtsvikt (HF) är en epidemisk sjukdom som ökar i prevalens med åldern och innebär en dålig prognos. Diagnosen av HF kräver både närvaro av typiska symtom och strukturella eller funktionella förändringar i hjärtat. En tidig identifiering av individer med hög risk att utveckla HF kan potentiellt förbättra prognosen. Det finns för närvarande inga tillförlitliga prediktionsmodeller av HF som kan användas i daglig klinisk praxis. EKG är ett enkelt och lättillgängligt diagnostiskt verktyg, men dess användbarhet för screening av framtida HF är fortfarande oklar.

Förmaksflimmer (AF) är en vanligt förekommande arytmisjukdom med ökad risk för stroke och HF. En tidig modifiering av riskfaktorer för AF kan minska incidensen av AF och förbättra prognosen., Förmakskardiomyopati, definerad som strukturella och/eller funktionella förmaksförändringar, är associerad med hjärt-kärlsjukdomar oberoende av AF och samtidigt ökar risken för utveckling av AF. EKG-förändringar kopplade till förmakskardiomyopati skulle därför kunna vara användbara i prediktionsmodeller för AF och även för HF.

Samtliga fyra studier som ingår i denna avhandling är baserade på Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) studien med 15 års uppföljning. PIVUS-studien startade 2001 och bjöd in alla 70 år gamla individer från Uppsala att delta. Av 2025 inbjudna lämnade 1016 personer, av vilka var 50% kvinnor, sitt medgivande för deltagandet. Anamnesen inklusive aktuella läkemedel togs och en kardiovaskulär undersökning inklusive blodtryck, 6-avlednings-EKG, 2-dimensionell ekokardiografi och blodprovstagning för biomarkörer utfördes på alla vid första besöket. En förnyad undersökning gjordes vid 75 och 80 års ålder, dvs efter 5 och 10 år enligt samma protokoll med undantag av EKG, som användes endast för detektion av AF.

Efter tillämpning av exklusionskriterier på PIVUS-populationen analyserades data på 836 personer med avseende på incident HF (Studie I och III-IV) och 877 personer med avseende på AF (Studie II). De 2 första studierna (I-II) testade om det fanns en korrelation mellan förmaksrelaterade EKG-variabler i avledning V1: P-vågsduration, P-vågsamplitud och PR-intervall till framtida HF och framtida AF. Cox proportional hazard-analys användes som statistisk metod i dessa 2 studier. Studie III använde sig av ”random forest”, en

maskininlärningsmetod för att relatera 132 EKG-variabler i 6 avledningar till framtida HF. EKG-variablerna av störst betydelse (Figur 2, studie III) lades sedan till de traditionella riskfaktorerna för HF (kön, systoliskt blodtryck, antihypertensiv behandling, rökning, genomgången hjärtinfarkt, AF före HF-diagnos, body mass kvot [BMI]) och en ny prediktionsmodell för HF skapades. Prestanda för denna modell avseende prediktion av HF jämfördes sedan med prestanda för en modell baserad på enbart traditionella riskfaktorer. Studie IV testade om låg frekvens/hög frekvens (L-F/H-F) kvot, ett mått på variabiliteten av hjärtfrekvensen (HRV) var relaterad till framtida HF och om ett tillägg av L-F/H-F-kvoten till traditionella riskfaktorer för HF kunde förbättra modellens prediktiva prestanda.

En kort P-vågsduration i V1 var signifikant associerad med framtida HF (Studie I), vilket var ett nytt fynd. En kort P-vågsduration i V1 var också signifikant associerad mad utvecklingen av AF (Studie II), vilket bekräftade resultaten från en stor dansk studie. En ökad nivå av relaxin innan utvecklingen av AF och HF var den hypotetiska mekanismen bakom dessa resultat. Av 134 EKG-variabler hade en hög variation av R-vågsamplituden det bästa prediktiva värdet för HF, vilket kan indikera en dominans av den sympatiska aktiviteten före HF-diagnosen (Studie III). Låg L-F/H-F-kvot var en annan stark prediktor för HF, vilket också indikerade en dominans av den sympatiska aktiviteten före utvecklingen av HF (Studie IV). Tillägget av de 8 EKG-variablerna de traditionella riskfaktorerna för HF resulterade i en signifikant förbättring av den prediktiva prestandan av modellen med 11,7 %, vilket var den högsta förbättring som hittills rapporterats för EKG-variabler (Studie III). Ett tillägg av L-F/H-F-kvoten till traditionella riskfaktorer för HF förbättrade modellens prediktiva prestanda med 3,3 % (Studie IV).

10.1.1.1 Slutsatser

En P-vågsduration är en enkel ECG variabel, lämplig för upprepade mätningar och potentiellt användbar för att hitta individer med hög risk att utveckla HF eller AF. Dessutom kan utvalda ECG variabler och HVR variabler som tillägg till traditionella riskfaktorer öka prestanda av modeller som används för att prediktera framtida HF hos äldre individer och på detta sätt förbättra prognosen.

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